DEVELOPING AND EVALUATING A COMPLEX INTERVENTION IN STROKE: USING VERY EARLY MOBILISATION AS AN EXAMPLE

Louise Eisten Craig

BSc (hons) in Physiotherapy

Thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD)

Health Economics and Health Technology Assessment

Institute of Health and Wellbeing

University of Glasgow

May 2013

Abstract

Background: Complex interventions, those that incorporate multiple interacting components, are difficult to define, measure and implement. The aim of this research was to develop and evaluate the complex intervention, very early mobilisation (VEM) in acute stroke care. The clinical effectiveness and cost-effectiveness of VEM were evaluated whilst simultaneously considering the implications for future implementation.

Methods: A mixed methods approach was used: systematic review, predictive modelling, observational study design, individual patient data meta-analysis, qualitative methods and economic evaluation. Statistical models to accurately predict mobility post-stroke were developed. A multicentre observational study was conducted to establish pre-implementation activity levels of acute stroke patients. Data from two completed and comparable feasibility trials were used to estimate the clinical and economic impact of VEM. A qualitative process evaluation was conducted to identify the barriers and facilitators to implementing VEM, if shown to be effective.

Results: Two predictive models were developed with age and stroke type common factors to both. Pre-implementation activity levels were low. Patients who underwent VEM were 3-times more likely to be independent at 3 months than were standard care (SC) patients. The incremental cost-effectiveness ratio associated with VEM in comparison to SC indicated VEM to be potentially cost-effective from a societal perspective. Barriers and facilitators identified for each stage of the stroke pathway and a set of HCPs' beliefs towards VEM were formulated.

Conclusions: This research has adhered to current guidance provided by the Medical Research Council to develop and evaluate VEM. The clinical effectiveness and cost-effectiveness of VEM were estimated. The ongoing A Very Early Rehabilitation Trial phase III will provide definitive evidence for the effectiveness of VEM and the wider consequences for stroke care. This research has provided the support and the foundations for the development of a clear implementation strategy for VEM.

Executive Summary

Background

The socio-economic impact of stroke is global and vast. Stroke accounts for 10% of deaths worldwide.[1] Those who survive may be left with significant limitations and restrictions in activities of daily living (ADL). Rehabilitation post-stroke aims to increase activity and participation. The optimum time to commence rehabilitation post-stroke and the intensity of rehabilitation to provide have been long-standing questions in the stroke research community.

Stroke rehabilitation is a complex intervention and although recommended in clinical guidelines[2] it remains controversial and lacks definition.[3] A key feature of rehabilitation is mobilisation. Mobilisation is defined as "out-of -bed physical activity" which may include transferring, for example, on or off the toilet, sitting out of bed, standing and walking.[4] Complex interventions, those that incorporate multiple interacting components, are difficult to define, measure and implement. Very early mobilisation (VEM) is an example of a complex intervention in acute stroke care. A Very Early Rehabilitation Trial (AVERT) phase III is currently underway to determine the clinical and cost-effectiveness of VEM, however, the results are not due until 2013. Even if the AVERT phase III shows positive findings in support of VEM, it will remain unclear how best to implement the intervention into routine practice.

The aim of this research was to develop and evaluate a complex intervention in acute stroke by adopting the Medical Research Council (MRC) complex intervention framework as the methodological approach and using VEM as the clinical example. The clinical effectiveness and cost-effectiveness of VEM were evaluated whilst simultaneously considering the implications for future implementation. The objectives of the research are fully explained on Page 33.

Methods

A systematic and staged approach was adopted to address the aim of this research based on the recommendations available from the MRC for the development and evaluation of complex interventions.[5] As recommended in this guidance a combination of methods were used: systematic review, predictive

modelling, observational study design, individual patient data meta-analysis (IPD MA), qualitative methods and economic evaluation.

Systematic review and predictive modelling

The Glasgow Royal Infirmary Stroke Register was used to develop statistical models for use to accurately predict independent walking 30 days post-stroke. Three methods were used to inform factor selection for model development: systematic review (Model 1), clinical opinion (Model 2) and univariate analysis (Model 3). Backward stepwise regression was used to identify significant independent predictors. Calibration plots, goodness to fit and receiver operating characteristic (ROC) curves were used to test model properties. The predictors identified were used to adjust for case-mix in the observational study.

Observational study design

A cross sectional multicentre observational study was conducted to establish a pre-implementation level of physical activity in acute stroke patients recruited from a Scottish healthcare setting. Novel and established methods to monitor activity were used and compared: accelerometry, a method considered novel in this population, and a behavioural mapping technique. Patients were followed-up at three and six months to assess the relationship between activity levels in the acute stages and function at three and six months. The primary outcome was the proportion of time spent upright.

Individual patient data meta-analysis

An IPD MA using data from two completed and comparable stroke rehabilitation trials (AVERT phase II and the UK Very Early Rehabilitation or Intensive Telemetry after Stroke [VERITAS]) was undertaken to estimate the clinical impact of VEM. The primary outcome was independence at three months. Secondary outcomes assessed at one week were as follows; level of stroke impairment, immobility-related complications and excessive fatigue.

Qualitative process evaluation

A qualitative process evaluation was conducted to identify the barriers and facilitators to implementing VEM, and to establish healthcare professionals' (HCPs) beliefs towards VEM. Doctors, nurses and therapists currently working in

acute stroke units (ASUs) in Scotland were invited to participate in a multidisciplinary focus group or a semi-structured interview. Data were analysed thematically.

Economic evaluation

A systematic review was conducted to identify the approaches used for the economic evaluation of stroke rehabilitation. Informed by the findings from this review, a cost-consequence analysis (CCA) and cost-effectiveness analyses using data from AVERT phase II and VERITAS were conducted to model the economic impact of VEM. For the cost-effectiveness analyses incremental cost-effectiveness ratios (ICERs) were calculated, where appropriate. One-way sensitivity analyses were performed on key unit costs by varying one measure at a time.

Results

Baseline factors predictive of mobility after stroke

Two predictive models were developed and validated using registry data. The final Model 1 consisted of the factors identified by the systematic review and Model 2 and Model 3 consisted of the same factors identified by both univariate and clinical opinion. Age and stroke type were factors common to both models. In addition, Model 1 identified level of consciousness and leg power and Model 2 identified living arrangements of admission, level of severity, level of disability and level of ADL. Models were very accurate in distinguishing patients who will or will not walk independently (area under ROC curve was 0.80 for Model 1 and 0.87 for Model 2).

Baseline levels of activity in acute stroke patients

Sixty-six patients were recruited to the observational study from three hospitals. The median time from stroke onset to the day of monitoring was 5.5 days. This study provided a precise estimate of the time spent upright (standing or walking) in a sample of acute stroke patients (8.2%; 95% confidence interval [CI], 6.2 to 10.1). The majority of total upright time was the result of short episodes of < 10 minutes spent in upright activity. The opposite pattern was observed for sedentary (sitting or lying) events whereby the majority of total sedentary time was accumulated in prolonged periods of time.

Clinical impact of very early mobilisation

All patients in AVERT phase II (n = 71) and VERITAS (n = 32) were included in the IPD MA. Patients who underwent VEM were three-times more likely to be independent at three months than were standard care (SC) patients (adjusted OR 3.11, 95% CI, 1.03 to 9.33). The risk of experiencing immobility-related complications at one week for VEM patients remained significantly lower than that of SC patients (adjusted OR 0.23, 95% CI, 0.07 to 0.71). The odds of excessive fatigue were not higher for VEM patients than for SC patients after adjustment of baseline factors (adjusted OR 0.79, 95% CI, 0.27 to 2.31). The reduction in the level of stroke severity was non-significant (adjusted coefficient -0.59, 95% CI, -2.44 to 1.27).

Barriers, facilitators and beliefs of very early mobilisation

Thirty-one HCPs (17 therapists, 10 nurses and four doctors) across seven hospital sites, of which three sites were actively recruiting to AVERT phase III, participated. The barriers most frequently identified to mobilising a patient within 24 hours included medical instability, perceived risks of mobilisation and the time of admission to the stroke unit. The facilitators most frequently identified to mobilising a patient within 24 hours included the belief that bed rest delays recovery, early admission to the ASU and early team communication. A set of beliefs towards VEM currently held by HCPs were formulated.

Economic impact of very early mobilisation

Twenty-one studies that had conducted an economic evaluation of stroke rehabilitation were included in the systematic review. The economic evaluations in the majority of these studies were inadequate based on their ability to identify, measure and value all resources and benefits pertinent to the complexity of stroke rehabilitation. On investigating the economic impact of VEM, a CCA was conducted to overcome this limitation and identify the wide-reaching effects. The ICER associated with VEM in comparison to SC was an additional £203 per additional patient achieving independence. The ICER calculated suggests that VEM is potentially cost-effective when considering the National Institute of Health and Clinical Excellence threshold of £20,000 to £30,000.

Discussion

Strengths and limitations of the methods used

This research has adhered to current MRC guidance for the development and evaluation of complex interventions. Explorative modelling techniques, evidence synthesis of best-available data and alternative methods to randomised controlled trials have been used.

Recommendations based on the finding of the two systematic reviews, where possible, were applied in subsequent predictive and economic modelling. The systematic reviews involved comprehensive searches of electronic databases and sources of grey literature, and were conducted in accordance to Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines. The final development of the predictive models did have limitations. The selection of factors was based on the opinions of only two clinical experts. A delphi-method where a panel of experts are used to provide consensus would have provided a more robust approach. Additionally, the models were not externally validated or evaluated in clinical practice.

Novel and established methods for monitoring activity were used and compared in the observational study. The integration of the accelerometer (AC) data with behavioural mapping data not only provided objective data on patient location and stroke processes but also offers a model of analysis for use in future studies. Despite synchronising the AC data with the observational data, no firm conclusions can be drawn about the accuracy of the *activ*PAL™ in detecting stepping as this was not a validity study.

The use of evidence synthesis to increase statistical power and provide information not available in the data sets has been of value in determining the clinical and economic impact of VEM. However, the sample was too undersized to make final conclusions about the clinical effectiveness and cost-effectiveness of VEM.

The findings from the qualitative process evaluation are representative of a relevant sample of HCPs working in acute stroke care. Triangulation of data (using the observational data and the qualitative data) highlighted discrepancies

between what staff believe they do and what they actually do, an important consideration when interventions involve changing current practice and in this early stage of implementation. The main limitation of this qualitative analysis is the lack of use of a theoretical framework which may have assisted in identifying the determinants of change and if those determinants are modifiable. Additionally, no nursing assistants participated in the focus groups and as it is this group of staff who deliver a large proportion of patient care and are involved in the day-to-day mobilisation of patients this is considered a limitation.

Interpretation of findings

The predictive models developed have not been evaluated in clinical practice, such as in a cluster randomised trial, therefore cannot yet be recommended for use in clinical practice. The models could be used in clinical audits, to compare patient outcomes in observational studies or to inform the stratification of patients in rehabilitation trials.

The clinical problem of low levels of activity in acute stroke patients has been confirmed in a Scottish healthcare setting; however, the prolonged periods of time spent in sedentary behaviour may be more cause for concern. This observational data offers a rich data source to assess the impact of new activity-based rehabilitation interventions or to identify changes in practice over time.

Given the small sample size of the individual studies included in the IPD MA this should only be considered as an illustration of the method, rather than allowing any confident deductions to be made regarding the effectiveness of VEM. The use of IPD MA in complex intervention research has highlighted the value of researcher collaboration with deliberate matching of protocol and outcome measures to allow data from two similar trials of methodological quality to be combined.

The barriers and facilitators identified, and the set of HCPs beliefs formulated can be used to explain current mobilisation practice. Problems areas and optimum ways of working have been identified and explored. This is an essential stage in changing practice of HCPs. The focus should now be on developing

tailored implementation strategies specific to each stage of implementation (dissemination through to sustainability).

The systematic review of economic studies highlighted the need for the adoption of a wider cost and benefit perspective beyond that of the health service in the economic evaluations of complex interventions such as stroke rehabilitation. Early supported discharge and interventions such as VEM are associated with a shift of care from the healthcare system to the community and patients themselves which may result in more 'out of pocket' expenses for patients and informal carers. Therefore, where the focus of the economic perspective is health outcome it is also important to consider the consequences for other people such as informal carers in addition to the patient.

Conclusion

A number of research methods were used including evidence synthesis, observational study design, qualitative methods and economic evaluation to develop and evaluate VEM. Very early mobilisation was shown to be potentially clinically effective for a number of key clinical outcomes and potentially cost-effective from a societal perspective. Access to the patient within 24 hours and medical instability were considered by staff to be the main barriers to implementing VEM in real-life.

The AVERT phase III trial will provide definitive evidence about the clinical and cost-effectiveness taking into account the wide clinical and cost implications of VEM. Only after this can the trial make recommendations about the use of VEM in acute stroke care and can the real-life implementation begin. This research has provided the support and the foundations for the development of a clear implementation strategy for VEM.

List of Tables

List of Figures

Acknowledgements

I am indebted to the Stroke Association who has funded me for the last three years to enable me to conduct this research. I would like to thank my principal supervisor, Dr Olivia Wu, Associate Professor Julie Bernhardt and Professor Peter Langhorne for all their help, encouragement and guidance whilst undertaking this research. I would also like to thank the following people and organisations for their contributions:

The patients and their family members who participated in the observational study.

The physiotherapists who conducted baseline assessments as part of the observational study.

The Stroke Research Network (SRN) who adopted the observational and qualitative studies and to the SRN Network research nurses for assistance in identifying suitable patients for inclusion to the observational study.

Professor Malcolm Granat (Glasgow Caledonian University) who provided the *activ*PALs™ to allow me to conduct the observational study.

Jan Chamberlain (Florey Neuroscience Institutes) who processed the case report forms for the behavioural mapping component of the observational study.

Associate Professor Julie Bernhardt and Professor Peter Langhorne for providing the trial data required to conduct the individual patient data meta-analysis and registry data to develop the predictive models.

The healthcare professionals who participated in the qualitative study.

Dr Nicola Burns (University of Glasgow) for her advice and discussions during the analysis of the qualitative data.

Dr Rebecca Shaw (University of Glasgow) for her guidance to conduct the qualitative component of this work.

Author's Declaration

I declare that, except where explicit reference is made to the contribution of others, that this dissertation is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Chapter two

I conducted the systematic review which involved developing the protocol, search strategies, running the searches in the databases, hand-searching and screening of references. I cleaned and analysed the registry data to develop the predictive models.

Professor Peter Langhorne cross-checked decisions made when screening references for inclusion and data extracted.

Chapter three

I co-ordinated the observational study which involved gaining ethical and management approvals for two health board areas, recruiting patients, conducting the protocols and follow-up of patients. I completed online training in and conducted the National Institute of Stroke Severity and the Modified Rankin Score patient assessments at baseline. I entered, coded and analysed the observational data.

The study was adopted by the Scottish SRN and the National Institute of Health Research Age and Ageing specialty group. The stroke research nurses assisted in the identification of patients. The SRN research nurses recruited patients only when the researcher was unable to do so. Physiotherapists at the participating hospitals completed the Mobility Scale for Acute Stroke baseline assessment.

Chapter four

I obtained, cleaned, pooled and analysed the trial data for meta-analysis.

Chapter five

I co-ordinated the qualitative study which involved gaining ethical and management approvals for three health board areas, recruiting HCPs and

conducting the interviews and focus groups. I transcribed four interview recordings. I coded and analysed the qualitative data.

First class secretarial services transcribed nine interview recordings. The study was adopted by the Scottish SRN. Dr Nicola Burns coded a subset of transcripts.

Chapter six

I conducted all aspects of the systematic review. I applied the costs to the trial data and performed the cost-consequence and cost-effectiveness analyses.

Dr Olivia Wu cross-checked decisions made when screening references for inclusion and data extracted.

To date, the following papers from this thesis have been submitted, accepted for publication or have been published:

Craig LE, Wu O, Bernhardt J and Langhorne P. Predictors of poststroke mobility: systematic review. International Journal of Stroke. 2011; 6 (4) 321-327.

Craig LE, Bernhardt J, Langhorne P and Wu O. Early mobilisation after stroke: an example of an individual patient data meta-analysis of a complex intervention. Stroke. 2010; 41(11) 2632-6.

Craig LE, Wu O, Bernhardt J and Langhorne P. Considerations for economic evaluation of complex interventions: a systematic review in stroke rehabilitation. International Journal of Stroke. 2013; doi: 10.1111/ijs.12041

Craig LE, Burns N, Shaw R, Bernhardt J, Langhorne P and Wu O. The barriers and facilitators to implementing very early mobilisation in acute stroke care: a qualitative process evaluation. Re-submission to Implementation Science, 2013.

The following abstracts from this thesis have been presented at conferences:

Craig LE, Bernhardt J, Wu O and Langhorne P. Accelerometry to monitor the patterns of activity in acute stroke patients. World Congress on Active Ageing, August 2012.

Craig LE, Bernhardt J, Wu O and Langhorne P. Using accelerometry to monitor the patterns of activity in acute stroke patients. European Stroke Conference, May 2012.

Craig LE, Bernhardt J, Wu O and Langhorne P. Using researcher observation to monitor process indicators in acute stroke care. European Stroke Conference, May 2012.

Craig LE, Bernhardt J, Wu O and Langhorne P. Using a process evaluation to identify the barriers and facilitators to implementing a policy of very early mobilisation in acute stroke care. European Stroke Conference, May 2012.

Craig LE, Wu O, Bernhardt J and Langhorne P. A systematic review of economic studies in stroke rehabilitation. European Stroke Conference, May 2012.

Craig LE, Bernhardt J, Wu O and Langhorne P. Understanding the challenges of changing behaviour of healthcare professionals working in acute stroke care. Medical Research Council Population Health - Methods and Challenges Conference, April 2012.

Craig LE, Bernhardt J, Wu O and Langhorne P. A process evaluation to identify the barriers and facilitators to implementing a policy of very early mobilisation in acute stroke care. Medical Research Council Population Health - Methods and Challenges Conference, April 2012.

Craig LE, Bernhardt J, Langhorne P and Wu O. Early mobilisation and the recovery of mobility in acute stroke: results from a pooled analysis of two randomised controlled trials. European Stroke Conference, May 2011.

Craig LE, Wu O, Bernhardt J and Langhorne P. Developing and accessing the performance of three prognostic models in predicting independent walking 30 days post stroke. UK Stroke Forum, December 2010.

Craig LE, Bernhardt J, Langhorne P and Wu O. Individual patient data meta-analysis of complex interventions – an example with early mobilisation in stroke. European Society for Medical Decision Making Conference, June 2010.

Craig, LE, Bernhardt J, Langhorne P and Wu O. Early mobilisation in stroke: a pooled analysis of two randomised controlled trials. European Stroke Conference, May 2010. **Travel was funded** by a Scientific Networking Award, University of Glasgow.

Abbreviations

AC	Accelerometer
ADL	Activities of Daily Living
ASU	Acute Stroke Unit
AVERT	A Very Early Rehabilitation Trial
BI	Barthel Index
BMT	Behavioural Mapping Technique
CCA	Cost-Consequence Analysis
CEA	Cost-Effectiveness Analysis
CI	Confidence Interval
CUA	Cost-Utility Analysis
CRF	Case Report Form
CT	Computed Tomography
DCE	Discrete Choice Experiment
HCPs	Healthcare professionals
HRQoL	Health Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
ID	Identification Number
IPD	Individual Patient Data
IPD MA	Individual Patient Data Meta-Analysis
ICF	International Classification of Functioning, Disability and Health
IQR	Interquartile Range
MRC	Medical Research Council
MeSH	Medical Subject Headings
METs	Metabolic Equivalent
mRS	Modified Rankin Scale
MSAS	Mobility Scale for Acute Stroke
MDT	Multidisciplinary Team
MRI	Magnetic Resonance Imaging
NIHSS	National Institutes of Health Stroke Scale
NICE	National Institute of Health and Clinical Excellence
NPT	Normalisation Process Theory
OCSP	Oxfordshire Community Stroke Project

OR	Odds ratio
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
RMI	Rivermead Mobility Index
ROC	Receiving Operating Characteristic
SC	Standard Care
SD	Standard Deviation
SSS	Scandinavian Stroke Scale
SRN	Stroke Research Network
TACS	Total Anterior Circulation Syndrome
UK	United Kingdom
VEM	Very Early Mobilisation
VERITAS	Very Early Rehabilitation or Intensive Telemetry after Stroke

1 Introduction

1.1 Stroke

Stroke is defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin." [6] There are two main types of stroke - ischaemic and haemorrhagic. Ischaemic stroke is the result of reduced cerebral blood flow with a consequent loss of neural functions. If the reduction in blood flow is sufficiently severe, a series of events occur at cellular level and leads to an infarction. Haemorrhagic stroke occurs due to rupture of a blood vessel in the brain. The signs and symptoms of stroke vary depending on the site affected and may include numbness or weakness of one side of the body, sudden loss of vision, dizziness, communication problems, problems with balance or co-ordination, or headache.

The socio-economic impact of stroke is global and vast. Stroke accounts for 10% of deaths worldwide.[1] In 2005 stroke caused an estimated 5.7 million deaths and without intervention the number of deaths is projected to rise to 6.5 million in 2015 and to 7.8 million in 2030.[7] The International Classification of Functioning, Disability and Health (ICF) can be used to classify the effects of stroke into three main domains: body functions or structures (such as mobility and cognition), activity (such as walking or reading) and participation (such as housework or employment).[8] Those who survive may be left with significant limitations and restrictions in activities of daily living (ADL). It has been estimated that approximately 15 million people suffer from a stroke, with five million left with residual disability. Stroke was ranked the seventh leading cause of disability-adjusted life-years lost in 2002 with this to increase to sixth in 2030.[9] This disability-adjusted life-years metric was developed by the World Health Organisation and measures the global burden of disease integrated health life lost due to both mortality and living with disability. The costs associated with stroke prevention and treatment were significant. In the United States of America total costs accounted to $65.5 billion with direct costs contributing to 67% of these costs while the remaining 33% was due to indirect costs such as loss in productivity.[10] In Europe direct costs have been estimated as €18.5 billion

(68.5%) and indirect costs as €8.5 billion (31.5%).[11] The societal costs of stroke in the United Kingdom (UK) have been estimated as £8.9 billion a year, with direct costs accounting for approximately 50% of the total, informal care 27% and indirect cost 24%.[12] Due to the high burden of disability, much of post-stroke care relies upon rehabilitation interventions[13] and may absorb a high proportion of direct costs.

Stroke patients are usually admitted to hospital in the initial stages and receive treatment in a number of ways and in different settings. There is vast evidence that patients who receive organised care in a stroke unit are more likely to be alive, independent and living at home one year post-stroke.[14 15 13] Organised stroke unit care is provided by "multidisciplinary teams that exclusively manage stroke patients in a dedicated unit (stroke, acute, rehabilitation, comprehensive), with a mobile stroke team or within a generic disability service (mixed rehabilitation ward)".[13] The key features of organised inpatient stroke care are: i) co-ordinated multidisciplinary rehabilitation; ii) staff with specialist interest in stroke or rehabilitation; iii) routine involvement of carers in the rehabilitation process; and iv) regular programmes of education and training.[13] This existing evidence for stroke care underpins current national guidelines and strategy documents for the management of stroke patients.[2 16 17]

1.2 Rehabilitation post-stroke

Stroke rehabilitation is a major component of stroke care. Stroke rehabilitation is difficult to define[13] and has been broadly defined as "a problem solving process aiming at reducing the disability and handicap (promoting activity and participation) resulting from a disease."[18] The aims of stroke rehabilitation are as follows:

- To maximise the patient's role fulfilment and independence in their environment, all within the limitations imposed by the underlying pathology and impairments and by the availability of resources[19]
- To help the person to make the best adaptation possible to any difference between roles achieved and roles desired[19]

The ICF outlines nine domains of activity and participation which can provide the focus for rehabilitation efforts which include communication, mobility and self-care.[8] With respect to this framework, rehabilitation aims to maximise the individual's activity, participation and quality of life, and minimise impact on carers.

The process of rehabilitation involves assessment, goal-setting, delivering intervention based on individual needs and reassessment.[20] An understanding of the recovery of stroke is required to develop and plan rehabilitation interventions such as the timing of certain interventions. Spontaneous recovery is a result of brain repair or reorganisation and is believed to occur in the first three to six months after stroke. Statistical models suggest that although outcome is defined within the first weeks, post-stroke functional improvement has been found to extend beyond six months but at a reduced rate.[21 22]

1.3 Evaluation of stroke rehabilitation

Rehabilitation offers the opportunity to reduce the burden of disability; however, given that it is resource-intensive, it is essential to evaluate its clinical effectiveness and cost-effectiveness. Stroke units that incorporate rehabilitation have shown to be most beneficial in reducing death and dependency.[23] Stroke rehabilitation is a complex intervention and intricate to evaluate[13 24] as it involves a number of components, interactions and outcomes.[5 25] For example, an inpatient exercise-based intervention typically has an education and a prescribing component. It also relies on a number of different interactions between the patient and the therapist and their beliefs i.e. the patients' lifestyle beliefs and adherence to treatment. Outcomes in rehabilitation are non-linear and wide-reaching, and the intervention itself occurs within a complex system where variations in stroke care between different settings are known to exist.[26] Therefore, the evaluation of stroke rehabilitation poses challenges in identifying the individual and interdependent effects of components and choosing a realistic outcome measure.[27]

Further issues relating to the evaluation of interventions considered to be complex may include ensuring an appropriate level of standardisation when

delivering the intervention, avoiding treatment contamination and blinding of participants. Standardisation and the ability to control influencing factors are key factors of randomised controlled trials (RCT). This process of standardisation is more difficult in health care interventions. Hawe et al (2004) argue that it is not the components of the intervention that should be standardised such as an education package but rather the steps in the change process (referred to as the key functions).[28] These key functions can then take on different 'forms' according to local context yet achieve the same objective. The intervention that Hawe et al (2004) use as an example is a community intervention to prevent depression. The principles of this community intervention are to "improve detection, management and referral of patients in primary care", the standard form that this should take is "a series of three in-service training workshops to general practitioners with preset curriculums" but could vary in the delivery (function). For example, local authorities could be "provided with materials and resources to devise in-service training tailored to local schedules, venues, and preferred learning methods".[28] Rehabilitation provided to patients may differ according to capability and the intervention protocol may allow for some flexibility in how this it is delivered. Standardisation of the intervention and the monitoring adherence within a trial setting is raised in Chapter 4.

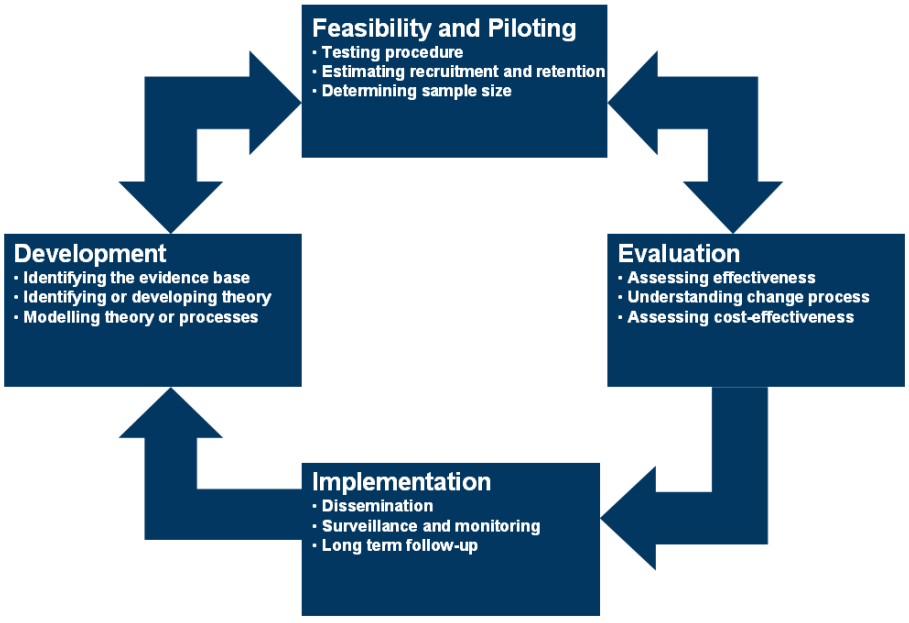
Treatment contamination is an issue for trials of rehabilitation which aim to change social behaviours. Cluster randomised trials, which involves separating the groups by location may prevent this, however intracluster correlations have implications for sample size. One way to overcome this is to integrate preventative measures to contamination into the intervention protocol. For example, not permitting trial staff to discuss the details of the intervention with non-trial staff. The issue of contamination and the impact this could have during and after the trial is discussed in Chapter 5.

Blinding patients and/or personnel delivering the intervention is often not possible in trials of complex interventions. Gaining ethical approval to blind both intervention and standard care (SC) patients may be an option and if it can be assumed that participants will not be able to distinguish between SC and the intervention. It may not be possible to blind the personnel involved in delivering the intervention to group allocation.

1.4 Developing and evaluating a complex intervention

In response to these challenges (such as multiple outcomes, standardisation, blinding and contamination) the UK Medical Research Council (MRC) developed a framework and a guidance document to assist the development and evaluation of non-pharmaceutical interventions or 'complex interventions' as they are more formally referred to.[28] The MRC defines complex interventions as those comprising of "a number of separate elements which seem essential to the proper functioning of the intervention although the 'active ingredient' of the intervention that is effective is difficult to specify."[5 29] The framework consists of four stages; feasibility/piloting, development, evaluation and implementation. The MRC guidance was recently updated and replaced the linear relationship between the four stages implied by the previous guidance with a cyclic model (Figure 1-1).[5] This permits interaction between the stages and encourages, for example, the implementation stage to be considered early during the other three stages rather than solely after the evaluation stage. This updated version of the MRC guidance also focuses more on implementation.

Figure 1-1 The Medical Research complex intervention framework



Adapted from "Developing and evaluating complex interventions: new guidance" [5]

The evaluation stage aims to assess the clinical effectiveness and cost-effectiveness of the intervention. The MRC framework advises researchers to select a study design most suited to the intervention under study with particular consideration given to the choice of outcomes and randomisation.[5] The framework also supports the use of appropriate methodologies other than RCTs to address the stages of the framework. The evaluation stage also highlights the importance of understanding the change process by conducting, for example, a process evaluation.

Process evaluations, using quantitative and/or qualitative methods, examine the way in which the interventions under study are implemented during the main evaluation and integrating these findings with the outcome data for the study allows for better interpretation.[5 30] Embedding a process evaluation to monitor the quality of implementation of the trial intervention, identify the inhibitors and facilitators for future implementation,[31] or explain variation in treatment effect for different locations or patients is crucial.[5] Process evaluations also allow for an evaluation of pre-existing contextual factors which should be studied simultaneously to the evaluation. Contextual factors may include healthcare systems (the physical environment and organisational structures), characteristics of the population and the disease under study as well as how these change over time.[32]

Implementation is defined as putting a guideline in place which involves effective strategies to overcomes barriers associated with change in clinical practice.[33] The increasing level and diversity of research relating to healthcare implementation has recently led to the development and use of the term 'implementation science'.[34] Implementation science has been defined as the investigation of methods, interventions and variables that influence adoption of evidence-based healthcare practices by individuals and organisations to improve clinical and operational decision making.[35] Implementation science also includes testing the effectiveness of interventions to promote and sustain the use of evidence-based healthcare practices.[34] The growing literature base presents several frameworks or models that refer to implementation. One model is Grol and Wensing's (2006) 'Model for Effective Implementation'.[36] This model uses a staged approach with the first phase aiming to identify relevant practice issues

(problems or best practice) and to conduct a thorough analysis of current practice. The later stages of the model consist of the process of setting operational change objectives, development of implementation strategies and then finally the operationalisation of an implementation plan.

An effective implementation strategy is critical for the successful uptake and sustainability of an intervention.[37] Effective implementation ensures the intervention is workable and integrated in everyday healthcare practice.[31] Studies have shown that about 30-40% of patients do not receive care according to the best available evidence. A recent Cochrane review aimed to assess the effectiveness of intervention strategies developed to overcome barriers to change on professional practice or patient outcomes.[38] An evidence-based approach is recommended to optimise effectiveness.[39] However, the evidence of which strategies are most effective remains inconclusive. This is further complicated by the limited generalisability of implementation strategies due to the heterogeneity of behaviours within the interventions, target audience and environment.[40] The application and effectiveness of such strategies to complex intervention research is unclear and little guidance exists.

In order to ensure that effective interventions are implemented smoothly and in a way that optimises compliance within an NHS organisation, appropriate monitoring of complex interventions in clinical practice is critical.[5] Monitoring the implementation of interventions reduces inequalities in care, improves quality of care and identifies the providers that are having difficulty executing parts of the intervention. Thus, it is important to monitor implementation early, simultaneously to evaluation and relative to the pre-implementation status to identify and solve problems.[41] It is essential to facilitate and demonstrate the implementation of evidence-based therapies using effective monitoring systems and by identifying relevant process indicators to audit care. For example, process indicators associated with rehabilitation may include the facilities and equipment that are in place (structures) and admission processes and the routine provision of mobilisation (processes).

1.5 Very early mobilisation: an example of a complex intervention

An example of a complex intervention in acute stroke rehabilitation currently under investigation in an international RCT is very early mobilisation (VEM). Very early mobilisation is defined as starting mobilisation (i.e. sitting out of bed, standing or walking) within 24 hours of onset of stroke symptoms and to continue this at frequent intervals throughout the patients stay in the acute stroke unit (ASU). Very early mobilisation encourages activity in these acute stages (within 14 days) and is delivered by the multidisciplinary team (MDT), most usually nurses, physiotherapists and occupational therapists. Very early mobilisation is a complex intervention due to its multidimensional nature. It has several interacting components i.e. an education component and a prescribing component. It incorporates a number of behaviours required by those delivering or receiving the intervention i.e. the number and complexity of skills used by physiotherapists to provide the intervention to stroke patients. The delivery of very early mobilisation is likely to be patient specific (tailored to the individual needs of the patient) and context specific (delivered within a dynamic and complex healthcare system). This has implications for the definition, standardisation and monitoring of VEM. Very early mobilisation has potentially wide-ranging and interacting effects, making the evaluation of VEM more challenging than that of a drug. Therefore, VEM is an appropriate illustration of a complex intervention and was used as the clinical example in this thesis.

Although early mobilisation of acute stroke patients is recommended in clinical guidelines,[2 42 43] VEM remains controversial and specific recommendations cannot be made until further evidence to guide practice is available. Mobilisation practices vary between countries with patients mobilised within 24 hours of symptom onset the convention in some countries while in others the mobilisation of patients routinely occurs four to seven days after stroke. Delaying mobilisation is based on the belief that cerebral perfusion pressure in the penumbra region needs to be maintained, therefore a horizontal position may increase intracranial blood flow to ischaemic tissue and reduce the infarct.[44] The emergence of the very early and more intensive rehabilitation intervention in humans has posed controversy.

Some development work of VEM has been undertaken in relation to establishing current activity levels of acute stroke patients and testing the feasibility of VEM in a clinical setting.[45 46] The cyclic nature of the MRC framework indicates that developing theory and an evidence base is an iterative process and should not end when commencing the main evaluation. Other areas of development may include exploring the predictable variations of important rehabilitation outcomes such as mobility (Chapter 2), establishing activity levels in other countries (Chapter 3) and investigating methods for monitoring activity-based interventions in real-life (Chapter 3).

Specific evaluation of VEM is more limited. One study has suggested that VEM is the single most distinctive characteristic of stroke unit care and the strongest predictor of improved outcome.[47] A Cochrane review which included studies that investigated VEM versus delayed mobilisation after stroke concluded that there was insufficient evidence to make recommendations on the use of VEM in stroke. The individual patient data from these included studies provide the opportunity to synthesis the best available evidence to estimate the clinical effectiveness and cost-effectiveness of VEM (Chapter 4 and Chapter 6, respectively).

A very early rehabilitation trial (AVERT) phase III is now well underway to determine the clinical and cost-effectiveness of VEM in stroke care.[4] Therefore, it is important that during these development and evaluation stages, early consideration is given to the implications for the future implementation of VEM, if the results of AVERT phase III are in favour of the intervention (Chapter 5).

Aim and objectives

Complex interventions, defined as those that incorporate multiple interacting components, are difficult to define, measure and implement. Early rehabilitation is a complex intervention and although recommended in clinical guidelines it remains controversial and lacks definition. A Very Early Rehabilitation Trial phase III is currently underway to determine the clinical and cost-effectiveness of VEM in acute stroke, however the results are not due until 2013. Even if the AVERT phase III trial shows positive findings in support of VEM, it will remain unclear how best to define, monitor and implement the intervention in routine practice.

The aim of this thesis was to develop and evaluate a complex intervention in stroke by adopting the MRC complex intervention framework as the methodological approach and using VEM as the clinical example. The clinical effectiveness and cost-effectiveness of VEM was evaluated whilst simultaneously considering the implications for future implementation.

To address this aim, developmental work was conducted to identify and comprehend the predictable variations in outcome post-stroke (Chapter 2). A pre-implementation level of physical activity was established and methods to monitor activity levels were investigated to allow the assessment of the future implementation of activity-based interventions such as VEM (Chapter 3). The evaluation stage investigated the clinical and economic impact of a VEM (Chapter 4 and 6). Evaluation also included the early stages of implementation as outlined in the Model for Effective Implementation.[36] Relevant practice issues (problems or best practice) were identified and an analysis of current practice was undertaken (Chapter 5). This thesis covers only the early stages of implementation and provides the basis for further work to address the implementation stage of the MRC framework which is focused on the longer-term aspects of implementation such as surveillance and longer-term outcomes (see Figure 1-1). The development and evaluation stages of this thesis have strong connections to implementation.

The objectives for this thesis are as follows:

Objective one

To identify, using statistical models, the baseline factors that are predictive of mobility early after stroke in order to understand the predictable variations in outcome.

Objective two

To establish, using an observational study design, pre-implementation physical activity levels in acute stroke patients in order to monitor the future implementation of activity-based interventions such as very early mobilisation.

Objective three

To estimate, using individual patient data from two completed feasibility studies, the clinical impact of very early mobilisation in order to understand the implications of implementing very early mobilisation.

Objective four

To establish, using a qualitative process evaluation study design, healthcare professionals' beliefs towards implementing very early mobilisation in order to understand the potential barriers and facilitators to very early mobilisation.

Objective five

To estimate, using economic evaluation, the economic impact of very early mobilisation in order to understand the implications of implementing very early mobilisation.

Structure of the thesis

The example of a complex intervention used throughout the thesis is VEM. There are seven Chapters: Chapters 3 and 5 use primary research methods and Chapters 2, 4 and 6 use secondary research methods. Chapters 2 to 6 have an introduction, methods, results, discussion and conclusion section. At the beginning of each Chapter an overview to justify the reason for the research contained in the Chapter and how it links to the previous Chapter and the topic of implementation. Chapter 1 provides an overall background to the main topics of this thesis; stroke rehabilitation, complex interventions, implementation and VEM. Chapters 2 and 3 included the research for the developmental stage of the MRC framework and address objectives one to two. Chapters 4 to 6 include the research for the evaluation stage of the MRC framework and address objectives three to five. Chapter 7 provides an overall conclusion for the thesis.

Chapter 1 introduces the clinical and economic impact of stroke, the importance of stroke rehabilitation and describes very early mobilisation, the example of a complex intervention, to be used in this thesis.

Chapter 2 consists of a systematic review of studies aimed at predicting mobility post-stroke and the development of statistical predictive models. This addresses **objective one.**

Chapter 3 is an observational study aimed to establish pre-implementation activity levels of acute stroke patients in order to monitor the future implementation of very early mobilisation. This addresses **objective two.**

Chapter 4 is an individual patient data meta-analysis of two feasibility trials previously conducted to investigate the clinical impact of very early mobilisation. This addresses **objective three.**

Chapter 5 is a qualitative process evaluation aimed to identify the barriers and facilitators to implementing very early mobilisation. This addresses **objective four.**

Chapter 6 consists of a systematic review of economic evaluations of stroke rehabilitation and an economic evaluation to model the economic impact of very early mobilisation. This addresses **objective five.**

Chapter 7 summaries the findings from each of the Chapters, discusses the clinical application of the available evidence and provides a critique of the methods used. The thesis also makes some suggestions for the future study of very early mobilisation and more generally, complex interventions.

2 Establishing baseline factors predictive of mobility after stroke

2.1 Introduction

Stroke is the most common cause of disability and in particular, reduced mobility is a major burden for stroke patients, their families and the health service.[48] One of the first questions a stroke patient will ask is if they will be able to walk again, and regaining mobility post-stroke is considered a primary goal of the stroke patient in early rehabilitation.[49 50] Therefore, accurate estimates of the likelihood and timing of recovery of mobility post-stroke is of great clinical relevance, providing vital information to healthcare professionals (HCPs), patients and their families; the ability to predict outcome in patients with acute stroke is of value clinically and in research.[51]

Currently there is no strong evidence to suggest that the effectiveness of rehabilitation interventions varies according to baseline factors. Understanding the predictable variations in outcome post-stroke will assist in informing future decisions about the suitability of certain rehabilitation interventions such as VEM. Therefore, a systematic review was conducted to identify baseline factors predictive of or associated with mobility early after stroke. The findings from a systematic review were used to develop statistical models to accurately predict mobility after stroke. The factors included in these statistical models were used to inform which data should be collected at baseline in the observational study (Chapter 3). Appropriate adjustment for patient case-mix can be made when investigating the relationship between baseline activity levels in acute stroke patients and function at three and six months (Chapter 3).

A number of definitions for mobility exist such as the "activity of moving from place to place, generally by walking or using a wheelchair".[52] The ICF define mobility as "an individual's ability to move about effectively in his surroundings."[8] More recently, a definition of mobilisation in stroke rehabilitation has been introduced; "out-of bed physical activity" which may include transferring for example on or off the toilet, sitting out of bed, standing and walking.[4]

A number of studies have been carried out to identify the predictors of functional outcome or the level of disability at six months after stroke.[53-55] Previous stroke, older age, urinary and bowel incontinence, and visuo-spacial deficits are among some of the factors shown to be predictive of function.[54 55] One of the earlier studies identified a significant relationship between independent early sitting balance and independent ambulation; however, this was based on a retrospective audit of 40 stroke patients and the timing of outcome assessment for patients varied.[56] A more recent prospective study of 217 inpatient rehabilitation patients concluded that outcome of mobility one year after stroke can be predicted by functional status, sitting balance, time between stroke onset and admission to rehabilitation and age.[57] Furthermore, functional status (measured using the Barthel Index [BI]) was the strongest predictor (explained 33% of the 48% total variance) which was in accord with others studies investigating the predictors of functional outcome.[58 59] In one systematic review, early predictive indicators for both ambulation and ADL up to one year after stroke were investigated.[60] Only studies that were of high scientific quality and were internally and statistically valid were included in this synthesis. Scientific quality was assessed according to internal, statistical and external validity using criteria used in a previous systematic review.[55] Predictors identified by this review from studies included urinary incontinence, initial disability in ADL and ambulation, severe paresis or paralysis, complications of ischemic stroke and apraxia. The use of ADL has been criticised as a poor measure of mobility, for failing to detect changes in early recovery of mobility following stroke, with independence in ADL often being achieved through compensatory movement.[61] Another review assessed predictive factors within one week of stroke onset and concluded that initial grade of paresis was the most important predictor of recovery of mobility at least three months after stroke.[62]

Research in stroke has aimed at identifying the determinants of function in the longer term rather than the return of mobility in the early stages.[63 64] An understanding of the factors that influence the recovery of mobility in the short term has particular bearing on the development and evaluation of rehabilitation practices in acute stroke. This is of particular importance considering the

increase in promising interventions that aim to improve recovery of mobility after stroke.[65] Controversy remains around the length of time post-stroke that recovery continues to takes place. The existing literature has primarily focused on three months, with the maximum motor recovery believed to occur in the first four weeks post-stroke;[66 67] however, there is some debate that recovery may continue for six months or more.[68]

Aim

The aim of this Chapter was to develop statistical models to accurately predict independent walking 30 days post-stroke.

2.2 Predictors of post-stroke mobility: a systematic review

A systematic review was undertaken prior to the development of the predictive models to review the methodological approaches and assess the quality of studies investigating the predictors of mobility post-stroke. As the findings of the systematic review will inform the predictive modelling the sections detailing the methods and findings of the systematic review are presented before the predictive modelling section.

2.2.1 Methods

Inclusion and exclusion criteria

The review included studies of patients who had a clinical or objectively confirmed diagnosis (such as Computed Tomography [CT] scanning) of stroke. Studies of mixed populations which included patients with brain injury or transient ischemic attacks in addition to stroke patients were excluded unless the results for patients with stroke were reported separately. Only studies that assessed baseline factors within one week of stroke onset were included.[51] The outcome of interest was mobility. This was defined by the ICF mobility items considered to be most relevant and commonly used in the assessment of mobility in acute stroke rehabilitation and included ambulation, transferring and stair

climbing. At least one of these mobility items had to be assessed within 30 days of onset of stroke. Studies that investigated upper limb mobility only were excluded. Due to the nature of this review, the study types of interest were observational cohort and case-control studies that identified factors predictive of or associated with mobility post-stroke. No limits were applied to the search with regards to language or year.

Search strategy and data extraction

The following electronic databases were first searched from inception to July 2010: AMED (from 1985), CINHAL (from 1981), EMBASE (from 1980), MEDLINE In-Process (from 1950), SIGLE (from 1985), Science Citation Index Expanded (SCI-Expanded), ISI Web of Science (Web of Knowledge; from 1900), LILACS (from 1982) and ZETOC (from 1993). The search was updated in March 2012. In order to identify relevant studies search strategies for each database (Appendix 1) were developed, with the assistance of an information specialist, using a combination of Medical Subject Headings (MeSH) and free text words such as 'mobility', 'prognosis', 'predictor' or 'determinant'. In addition, the references from the retrieved articles were hand searched for relevance and a citation search of Web of Science was conducted.

The titles and abstracts of retrieved references from the search were screened by the author to exclude obviously irrelevant studies. The full articles of studies that satisfied the inclusion criteria were reviewed and data extracted using a standardised data collection form. Extracted data and decisions were cross-checked with a second reviewer. Data extraction included full study characteristics – author(s), country of origin, date of publication and design. A description of the baseline factors collected, the outcome measures used and the timing of assessments were also recorded. Information from multivariate analysis models including the size and strength of effect (regression coefficients, odd ratios or p-values) were also noted. The methodological quality of the studies was assessed using a standard criteria which covers four domains:[51] external validity, internal validity, statistical validity and the evaluation of the model. These criteria were developed using the recommendations from the 'Task Force on Stroke Outcomes Research of Impairments, Disabilities and

Handicap'[69] which aimed to increase the methodological quality of studies of stroke outcome and comply with methodological principles laid out for predictive research.[70-72]

Originally, a meta-analysis was planned if compatible estimates of effect and variation were available. If homogeneity could be assumed the odds ratio (OR) or log ORs (from logistic regression outputs) would have been combined using the Mantel-Haenszel or inverse variance methods respectively.[73] In the absence of such summary data the independent variables under investigation were tabulated along with p-values.

2.2.2 Results

The total number of studies identified by the search was 11,120. Following initial screening of titles and abstracts, all duplicate and irrelevant studies were excluded, and the full-text articles of 65 studies were assessed in detail (Appendix 2). Overall, five studies met the selection criteria, and were included in the review (Table 2-1).[74-78] No further studies were included as a result of the update search run from July 2010 to March 2012 (Appendix 3). The studies were prospective cohorts studies ranging from 197 to 804 stroke patients, with the mean age of the patients ranging from 64.4 years to 74.4 years (based on data from four studies as one study did not report age). Although subarachnoid haemorrhage was a specific exclusion criterion in only two studies, none of the studies included any patients with subarachnoid haemorrhage.[75 76] The studies can be broadly divided into two types – studies that assessed the association between baseline factors and the outcome by univariate analysis [74 76 78] and those that evaluated the predictive value of baseline factors by developing a statistical model.[75 77]

All baseline information was collected on admission to the ASU with one study specifying a median onset to admission interval of 12 hours.[76] The mobility outcome measured by all studies was walking. Only two studies had fixed assessment points with the time to achieving a specific mobility outcome within a set follow up period recorded – one at seven days and the other at one month post-stroke.[75 77] Independent walking was defined as "walking speed of at least

1.5 meters per second" in one study, while a five-point scale ('normal' to 'bedridden') were used in another.[75 77] Two of the five studies were conducted at the same hospital site and described the pattern of recovery using four key areas of mobility (sitting balance, standing balance, 10 steps and 10-metre walk) according to the Oxfordshire Community Stroke Project Classification (OCSP).[74 78] In the remaining study the Scandinavian Stroke Scale (SSS) walking subsection was the outcome of interest.[76]

Table 2-1 Table of evidence for included studies

Author, location	Study Design	Inclusion (I)/exclusion (E) criteria	Age(SD)/ Female (%)	Factors (measure used)	Mobility Outcome	Outcome Time point
Friedman et al 1991 New Zealand	Prospective cohort (n=197)	**I** clinical definition of stroke **E** SAH	Overall figures not available	Age, sex, pre-stroke disability, prior stroke, initial level of consciousness, minimum arm and leg power (MRC Scale), cognitive performance (MMSE) homonymous hemianopia (confrontation of examiners fingers), visual extinction, line bisection error (200mm long line), constructional apraxia (ability to draw a house)	Independent gait (a walking speed of at least 1.5m/s)	Day 7, Month 1, 2, 3 and 4
Matsunga et al 1997 Japan	Prospective cohort (n=577)	**I** supratentorial infarction **E** bilateral infarction	64.4 (13.1) 165 (33.9%)	Age, sex, level of consciousness (4pt scale), severity of paresis (hemiparesis or hemiplegia), side of lesion (CT), size of lesion (CT)	Locomotion function (five point scale: normal, walk alone, walk with aids, wheelchair & bedridden)	One month post-stroke admission
Baer and Smith 2001 United Kingdom	Prospective cohort (n=238)	**I** infarct as confirmed by CT **E** intracerebral haemorrhage	71.8 (11.2) 93 (50.3%)	Stroke type - PACI (39.8%), LACI (26%), POCI (19.5%), TACI (14.6%) (OCSP, confirmed by CT)	Time in days to achieve 10 steps and 10m (standardised single 10m walking test) Time to complete a 10m walk (stopwatch)	Daily
Jorgensen et al 1995 Denmark	Prospective cohort (n=804)	**E** SAH	74.5 (10.8) 443 (53.9%)	Leg power (SSS)	Walking function (BI score (no walking function (0-5 points), walks with assistance (10 points), independent walking function (15 points)	Weekly until death or on discharge of rehabilitation. Mean los = 35 (SD = 41) days
Smith et al 1999 United Kingdom	Prospective cohort (n=238; 9 omitted due to death/coma)	**I** infarct or haemorrhage as confirmed by CT	69.7 (11.9) 119 (52%)	Stroke type - PACI (35.4%), LACI (26.6%), POCI (6.6%), TACI (19.2%)	Time to mobility milestones (including sitting balance, standing balance, walk)	Daily Mean LOS = 56.9 (SD = 67.7) days

SAH: Subarachnoid Haemorrhage; MRC: Medical Research Council; MMSE: Mini-Mental State examination; CT: Computerised Tomography; PACI: Partial Anterior Circulation Infarction; LACI: Lacunar Infarct; POCI: Posterior Circulation Infarcts; TACI: Total Anterior Circulation Infarct; OSCP: Oxfordshire Community Stroke Project; SSS: Scandinavian Stroke Scale; BI: Barthel Index; LOS: Length of Stay; SD: Standard Deviation

A total of 15 baseline factors were investigated in the studies included in the review: baseline demographics including age and sex; prior history including pre-stroke disability and prior stroke; and clinical determinants including arm power, cognitive performance, consciousness, constructional apraxia, homonymous hemianopia, leg power, stroke classification, size of brain lesion, severity of paresis, side of lesion and visual extinction (Table 2-2). Five of these baseline factors were tested in more than one study with age, severity of paresis and stoke type significantly associated with or predictive of walking in at least two studies. Stroke type was significantly associated with walking in two of the studies [74 78] although not in the study conducted by Freidman.[75] Two studies developed a predictive model and showed that sex was not predictive of walking while there was disagreement regarding the inclusion of the factor, level of consciousness. Arm power, cognitive performance, constructional apraxia, pre-stroke disability, previous stroke, side of lesion and visual extinction were also tested and found to have no predictive value.[75 77]

Overall, the studies did not meet the majority of the criteria for good predictive research (Appendix 4). All the studies provided descriptions of cohorts in relation to the inclusion and exclusion criteria used and all reported baseline demographics. Generally, the sample size used was considered appropriate with regards to the number of factors that were being investigated. In one study multivariate analysis was conducted only on a subset of patients who had not achieved independent walking at seven days,[75] resulting in an insufficient event per variable (EPV) ratio for the number of independent factors included in the model. Sample size was viewed appropriate if a study had at least 10 outcome events for each factor used in the predictive model. None of the predictive models were evaluated in the dataset used to develop the model or externally validated in an independent dataset. Studies did not use validated outcome measures designed to assess mobility [74 75 77 78] or used the walking subsection of a global assessment tool.[76] Two studies assessed mobility using four locally designed mobility milestones but did provide clear standardised descriptions of how these were assessed.[74 78]

Table 2-2 Baseline factors investigated by included studies

Factor	Friedman et al 1991	Matsunga et al 1997	Baer & Smith 2001	Jorgensen et al 1995	Smith et al 1999**
Age	✓(p=0.05)	✓(OR* = 1.25)			
Level of consciousness	×	✓(OR = 1.26)			
Size of brain lesion		✓(OR = 1.38)			
Severity of paresis		✓(OR = 1.21)			
Hemianopia	✓(p=0.02)				
Leg power	✓(p=0.03)			✓ (p<0.01)	
Sex	×	×			
Side of lesion		×			
Pre-stroke disability	×				
Prior stroke	×				
Minimum arm power	×				
Cognitive performance	×				
Visual extinction	×				
Constructional apraxia	×				
Stroke type	×		✓		✓

× Factor tested but not predictive ✓ factor tested and predictive or associated

* OR: Odds ratio was calculated from reported correlation coefficients

** Based on time to achieving mobility outcome (>30 days)

2.3 Development of predictive models

2.3.1 Methods

The Glasgow Royal Infirmary Stroke Register which contains baseline and outcome data for 1029 consecutive patients admitted to an urban teaching hospital between 2000 and 2002 was used to develop the predictive model. The mobility outcome used for the analysis was independent walking at 30 days post-stroke as measured by the subsection of the BI. Patients were excluded from the analysis if this data were not available.

The factors identified by the systematic review and present in the data set constituted Model 1. As the review identified a low number of studies investigating predictors in this early stage post-stroke two other methods were used to identify potentially predictive factors and thus developed two further predictive models; one based on factors selected by clinical opinion (Model 2) and the other using univariate analysis to select factors (Model 3). These methods of selecting factors for modelling avoid over fitting of the model which is associated with including all patient baseline factors in the model.[72]

Clinical opinion was obtained from a physiotherapist and a doctor. Baseline factors were listed, along with a description and the intention for inclusion/exclusion with reason for any exclusion stated, and provided for independent appraisal. Justified disagreement resulted in the factor being subsequently included or excluded accordingly. The reasons for exclusion were classified into three categories: 'irrelevant'; factors considered unlikely to be associated with the outcome, 'better measure available'; duplication of factors i.e. diabetic medication was excluded in favour of presence of diabetes. To reduce the number of factors only one blood pressure variable was included. Diastolic blood pressure was excluded as there is some evidence that diastolic blood pressure is measured less reliably than systolic blood pressure.[79] The third category was 'missing data' for factors with high levels of missing data (defined as missing for > 20% of patients) which may reflect that they are not easily collected in clinical practice.

Univariate analysis was conducted between the baseline factors and the outcome to determine inclusion for Model 3.[72 80] Categorical factors were either dichotomised (stroke type, side of lesion and housing arrangements on admission) or the number of groups were reduced (i.e. smoking status, level of disability). This was done to minimise the number of factors entered into the models in order to make the models as parsimonious as possible.[80] Continuous factors were categorised (i.e. level of stroke severity and ADL) using well-established cutoff points if data were not normally distributed and did not have a linear relationship with the outcome. It is recognised that dichotomising data can result in biases and loss of efficiency,[81] therefore the recommendation to categorise factors into three groups was adopted.[82]

Data on age were normally distributed and there was some evidence that the association between age and the outcome was linear. Systolic blood pressure on admission and systolic blood pressure measured between day one and two was dichotomised using the cutoff point $\geq$ 160 mmHg as there was no evidence that the association between blood pressure and the outcome was linear. The length of time from symptom recognition to admission was dichotomised at the median, again as the association between this factor and the outcome was not linear. Since the dependent variable in the data set was binary, logistic regression was the technique employed using backward stepwise regression to drop the least significant factors in turn. Odd ratios were calculated from the regression coefficients in order to convert to a natural scale and ease interpretation. A conservative level of significance ($p \leq 0.1$) was used to prevent omission bias both on univariate and multivariate analysis.

The performance of a predictive model should be assessed in terms of both calibration and discrimination.[83] Calibration was investigated by plotting the actual proportion of patients who walked independently at 30 days against the probability predicted by the model. To do this the prediction scores (calculated from the regression coefficients) were split into deciles and the mean predicted probability calculated for each group. The mean predicted probability was then plotted against the observed proportion along with 95% CI for each predictive score group. These calibration plots were accompanied by the Hosmer-Lemeshow test.[71] Although, calibration may allow patients to be advised of their

chances of walking it does not distinguish between those patients who will and will not walk independently.[84] It is the area under a receiving operating characteristic (ROC) curve which provides an assessment of how good the model is in discriminating between individuals with and without the outcome.[72] A ROC curve plots the sensitivity (proportion of true positive predictions) against 1 minus specificity (proportion of false positive predictions). An area of 0.5 implies a prediction that is not informative and considered no better than chance alone. The higher the area under the curve the better the model is at predicting the outcome.

2.3.2 Results

The patient baseline demographics and clinical factors are presented in Table 2-3. The total number of baseline factors stored in the data set was 103. Outcome data were available for 820 patients with 487 patients (59.4%) independently walking at 30 days post-stroke.

Table 2-3 Baseline demographics and clinical factors

	n(%)*	**n(%)***
Number of patients	**1029**	**820**
Age (mean, SD)	68.9 (13.2)	69.2 (12.6)
Female	518 (50.3)	406 (49.5)
Stroke risk factors		
Hypertension	492 (47.8)	405 (49.4)
Atrial fibrillation	115 (11.2)	98 (12.0)
Coronary heart disease	335 (32.6)	273 (33.3)
Diabetes	178 (17.3)	146 (17.8)
Current Smoker (yes)	365 (35.5)	289 (35.2)
Independent pre-stroke (mRS score 0-2)	823 (80.3)	667 (81.3)
Living arrangements on admission		
Home alone	337 (32.8)	287 (35.0)
Home not alone	605 (58.8)	470 (57.3)
Other	87 (8.5)	63 (7.8)
Stroke history		
Previous stroke	321 (31.2)	261 (31.8)
SSS score (median, IQR)	46 (31-54)	47 (35-55)
Oxfordshire classification		
TACS	231 (22.5)	150 (18.3)
PACS	351 (34.1)	302 (36.8)
LACS	287(27.9)	234 (28.5)
POCS	78 (7.6)	66 (8.1)
Unknown	82 (8.0)	68 (8.3)

* Entries are n (%), unless stated otherwise

mRS: Modified Rankin Score; NIHSS: National Institute Health Stroke Scale; TACS: Total Anterior Circulation Syndrome; PACS: Partial Anterior Circulation Syndrome; LACS: Lacunar Circulation Syndrome; POCS: Posterior Circulation Syndrome; SSS: Scandinavian Stroke Scale (a lower score indicate higher impairment)

Four out of the seven factors (age, stroke type, consciousness level and leg power) identified by the systematic review as significant predictors of mobility post-stroke were recorded in the data set and therefore constituted Model 1. The clinical experts identified 22 factors as potentially predictive of independent walking. This clinical appraisal process excluded 78 factors; better measure available (58.4%), irrelevant (27.3%), missing data (14.3%) (Appendix 5). On univariate analysis 32 factors were significantly associated with independent walking. A summary of the factors entered into the three models is in Appendix 6. The final factors included in Model 1 after stepwise regression analyses were age ($p < 0.01$), stroke type ($p < 0.01$), consciousness level ($p = 0.04$) and leg power ($p < 0.01$). The output from the model including regression coefficients and p-values is in Table 2-4.

Table 2-4 Results from multivariate analysis

Factor	Model coefficient	95% CI	p-value	OR
Model 1: systematic review (n=819)				
Age	-0.04	-0.05, -0.02	0.000	0.97
Stroke type (TACS)	-1.49	-1.96, -1.02	0.000	0.23
Consciousness (unaffected)	0.80	0.05, 1.55	0.036	2.23
Leg power (unaffected)	1.09	0.74, 1.44	0.000	2.98
Model 2: clinical opinion/univariate analysis (n=817)				
Age	-0.02	-0.04, -0.01	0.004	0.98
Living arrangement (alone)	0.40	-0.01, -0.82	0.056	1.50
Stroke type (TACS)	-0.52	-1.11, -0.08	0.088	0.60
Stroke severity (moderate)	-0.84	-1.38, -0.30	0.002	0.43
Stroke severity (severe)	-1.59	-2.62, -0.55	0.003	0.20
Disability (moderate)	-1.17	-1.76, -0.57	0.000	0.31
Disability (severe)	-3.20	-5.41, -0.99	0.004	0.04
Activities of daily living (moderate)	-0.61	-1.25, 0.03	0.064	0.55
Activities of daily living (severe)	-1.37	-2.50, -0.23	0.019	0.26

The dependent variable is independent walking measured at 30 days post-stroke. The independent factors included in the final multivariate models are listed in the first column. Stroke type, consciousness, leg power, living alone, severity, disability and activities of daily living were assigned a value of 1 if the condition in brackets was satisfied (in the absence of the condition the variable was assigned a 0).
Stroke severity was measured using the Scandinavian Stroke Scale; moderate: 26-42; severe: 0-25. Disability was measured using the Modified Rankin Scale; moderate: 4; severe: 5
Activities of daily living was measured using the Barthel Index; moderate: 3-9; severe: 0-2

Positive regression coefficients and an OR greater than one means the patient is more likely to be walking independently than the patients in the reference category (always coded 0) at one month. For example, the odds of independent

walking for a patient who is fully conscious (coded 1) on admission are 2.23 times the odds of independent walking for a patient who has a reduced consciousness level (coded 0). Similarly, negative coefficients and an OR less than one means the patient is less likely to be walking at one month. For example, a patient who has experienced a Total Anterior Circulation Syndrome, (TACS) (coded 1) the chances of independent walking are reduced by approximately 80% compared to a patient who had experienced any other type of stroke (coded 0). When developing models 2 and 3, the factors that remained after stepwise regression were the same (hereon referred collectively as Model 2). For Model 2, the predictors of walking after stroke following stepwise regression were age ($p < 0.01$), living alone on admission ($p = 0.07$), stroke type ($p = 0.09$), level of severity (overall p-value = 0.02), level of disability (overall p-value < 0.01) and level of ADL (overall p-value = 0.04)**.** In particular, patients with a high level of disability on admission had significantly reduced chances of walking independently at three months (OR 0.04, $p < 0.01$, 95% CIs -5.41- to -0.10). The CIs are wider than those of any other variable, indicating a degree of uncertainty, probably due to the lower number of patients in this group. The regression coefficients were then used to calculate a predictive score for individual patients (Box 1-1). These scores was then used to create the predictive score groups used to develop the calibration plots.

Box 1-1 Calculating predictive scores using regression coefficients

Calculating a predictive score from regression model to predict the probability of walking for a patient 30 days post-stroke

Predictive score = 2.01 + ((age x -0.04) + (stroke type x -1.50) + (consciousness x 0.80) + (leg power x 1.09))

The value of 2.01 is the intercept and the numbers each predictor is multiplied by is the corresponding estimated regression coefficient. The estimated regression coefficients are the log (odds ratios) for a change of 1 unit in the predictor.

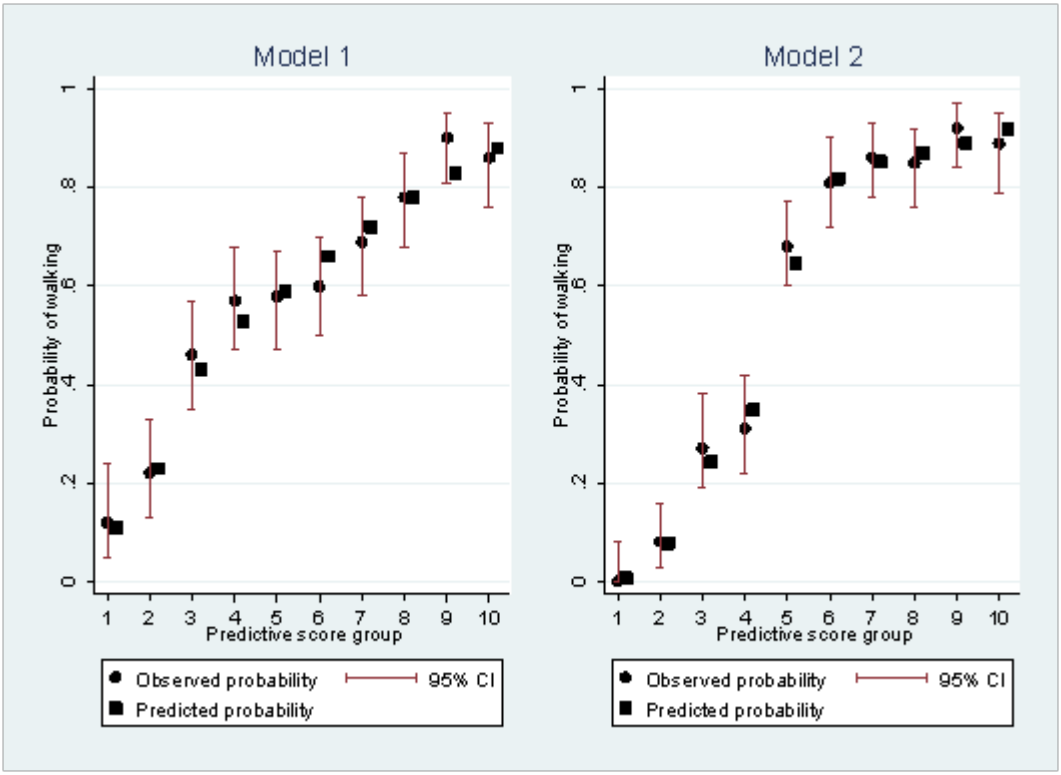
The predicted probability = exponential (predictive score) / (1+ exponential (predictive score))

For example, a patient aged 81 years classified as having a posterior circulation infarct, had reduced consciousness on admission and had normal leg power would have a predictive score of 0.23. Therefore, the predicted probability of independent walking for this patient is 0.56.

Adapted from Royston et al, British Medical Journal.[72]

The calibration plots for both models (Figure 2-1) show that the predicted probabilities (black squares) generated by the model fit well with the actual data (black circles). In Model 2 the increase in probability of walking that occurs between the predictive score groups five and six is likely to be due to the number of predictive score groups used or reducing the number of disability classifications. The p-value for the Hosmer-Lemeshow goodness of fit test was 0.31 for Model 1 and 0.83 for Model 2 showing that Model 2 has a better fit with the observed data than Model 1.

Figure 2-1 Calibration plots of predicted and observed probabilities



The predicted probabilities are represented by the black squares. The observed data are represented by the black circles.

When testing the discriminative properties of the model the ROC curve value was 0.80 for Model 1 (Figure 2-2) and 0.87 for Model 2 (Figure 2-3) showing that both models are better than chance alone in predicting independent walking at 30 days and are very accurate in distinguishing patients who will and those who will not walk independently at three months. The curve for Model 2 (Figure 2-1)

shows a steeper incline to the upper left hand corner of the graph indicating that a higher true positive rate can be achieved for the same true negative rate.

Figure 2-2 Receiver operating characteristic curve for Model 1

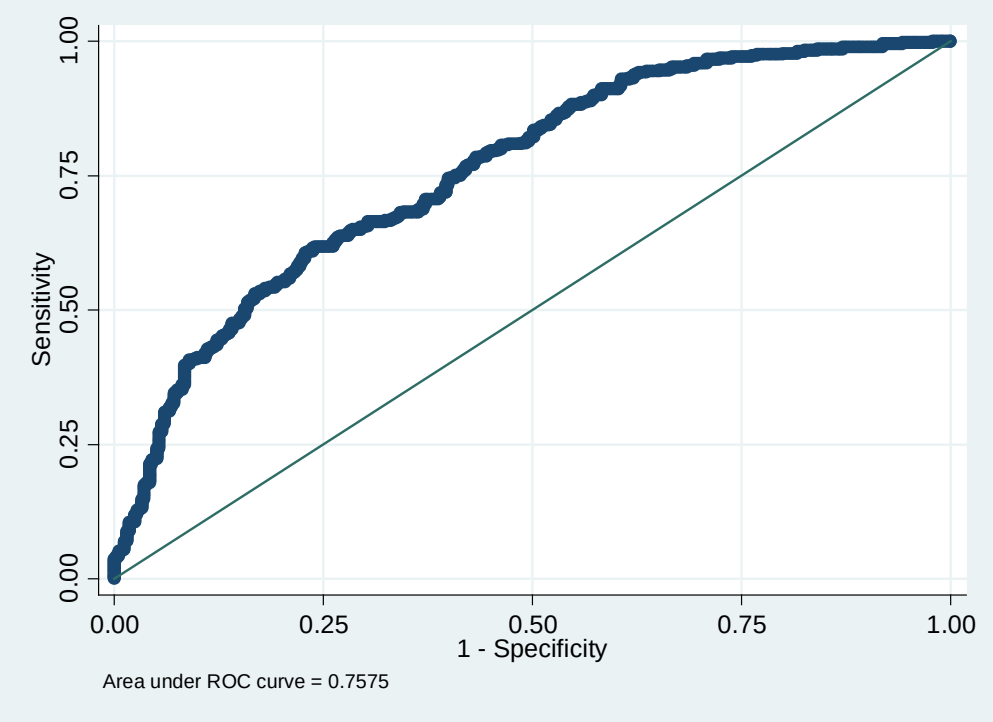
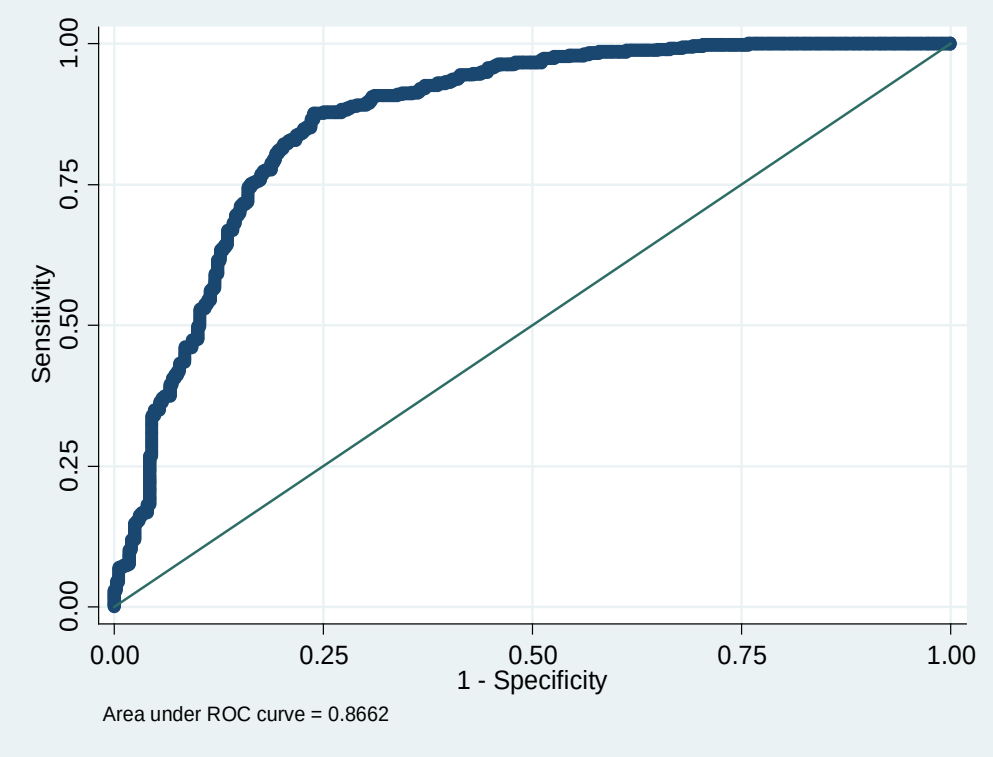


Figure 2-3 Receiving operator characteristic curve for Model 2



Sensitivity is the true positive rate. 1-specificity is the true negative rate.

2.4 Discussion

Summary of key findings: systematic review

This systematic review identified baseline factors assessed within one week post-stroke that may be of value in predicting the recovery of walking in the acute stages post-stroke. Age, the severity of paresis, the degree of leg power, presence of hemianopia, size of brain lesion and type of stroke were predictors of walking within 30 days post-stroke. Age, the severity of paresis and reduced leg power were each shown to be predictive in more than one study. It could be speculated that severity of paresis and the degree of leg power are measuring the same thing. The severity of paresis was classified as either hemiparesis or hemiplegia, while leg power was measured using an ordinal scale or a continuous scale. As it was unclear whether severity of paresis referred exclusively to lower limbs and the same assessment tool was not used it was decided that these two factors be presented using the original definitions. Age has been frequently noted to have a positive association with function in the longer term.[59 85] There was disagreement between the included studies as to whether level of consciousness and stroke type had any association with the recovery of walking. This may have been due to the differences in the measurement of these baseline factors and categorisation at the analysis stage. For instance, one study measured and analysed consciousness on a four point scale while another analysed this as a dichotomised factor (alert or not alert).[75 77] Also, the time point at which consciousness was assessed after stroke onset may have varied between the studies. One study specified that level of consciousness was assessed within three days after onset of stroke while the other study conducted baseline assessments during the first five days after stroke.[75 77]

The most commonly assessed mobility outcome was walking. Walking speed was used to define independent gait [75] and an unnamed five-point scale (ranging from ‘normal’ to ‘bedridden’) was used to define independent gait in the two studies that developed predictive models.[77] Two of the association studies were conducted at the same hospital site and described the pattern of recovery in four key areas of mobility (sitting balance, standing balance, 10 steps and 10-metre walk) according to the OCSP.[74 78] The remaining association study used the

SSS sub-section for walking.[76] Two studies used fixed assessment points with one study assessing patients at seven days and the other study assessing patients at one month post-stroke. The other studies did not have fixed assessment points and recorded the time to achieving a specific mobility outcome within a set follow-up period. [74 76 78]

The selection of factors for the two predictive models developed in the studies was based on univariate analysis. While it is common practice to include factors that are significant on univariate analysis it is also important to include those based on clinical opinion or are theoretically associated with the outcome. It has been speculated that variable screening based on statistical significance alone may lead to an unreliable model. For example, the presence of incontinence and balance impairment on admission are frequently cited as potential predictors of reduced mobility in the long-term.[86-91] These factors were not investigated or controlled for in any of the included studies. No attempt was made to assess the performance of the predictive models identified by this review by evaluating accuracy, discriminatory power or clinical applicability in other cohorts. In summary, the main limitations highlighted by this review were that factors may have been missed due to the method used to select variables and no attempts were made to validate the models that were developed.

Summary of key findings: predictive modelling

Considering the limitations identified by the review, existing registry data were used to develop and test suitable models to accurately predict independent walking 30 days post-stroke. Two final predictive models were developed in this study; one using the factors identified in the systematic review and available in the data set and a further model which was based on factors that had been selected by both clinical opinion and univariate analysis. Model 1 showed age, stroke type, consciousness and leg power to be predictors of walking one month after stroke. Model 2 showed age, living arrangement, stroke type, stroke severity, disability and ADL to be predictors of walking one month after stroke. The model based on clinical opinion and univariate analysis (Model 2) showed better agreement between the predicted and observed data than that of the model solely based on the systematic review (Model 1). Both models appeared to

be able to discriminate well between those patients likely to walk and those who were not likely to walk.

The predictive modelling component of this research aimed to overcome some of the methodological shortcomings highlighted by the systematic review. The development of predictive models used a structured approach to variable selection, reported a codebook for the baseline factors used in the model and assessed the performance of the models. The most appropriate method for variable selection is questionable. The factors finally included in Model 2 and Model 3 had been identified by clinical opinion and by univariate analysis suggesting that either one of the approaches is sufficient to select factors for inclusion. The comparison of these two methods with factor selection based purely on systematic review is limited in that not all the factors were available in the data set i.e. lesion size.

The number of factors entered into Model 3 was 32 which could be considered high. Using the EPV ratio of 10:1, as previously explained, at least 320 outcome events would be needed. This would mean that 603 patients would be required for an event rate of 53% (literature estimate[92]). Therefore, using this general rule the sample size of 817 is sufficient to assess the factors that were entered into the model. A common limitation in predictive modelling is the management of data sets where data on potential predictive factors may be missing. A standard approach to manage this is to conduct a complete case analysis whereby patients that have missing data are excluded from the analysis or to exclude the factors that have a high degree of missing data**.** There is little guidance to the extent of data that should be missing before it warrants exclusion, hence the use of a > 20% cut-off in this analysis. This could lead to the exclusion of a defined subset of patients i.e. for example, unconscious patients, where it has not been possible to ascertain their smoking habits. An alternative approach, multiple imputation, does not only increase the statistical power of the analysis but helps eliminate the bias associated with excluding patients in a complete case analysis or exclusion of factors with a high number of missing data.

Strengths and limitations

The number of studies eventually included in the systematic review from the search output was low (n = 5). The lack of distinction between motor and functional recovery in the neuromedical literature[67] and differences in definitions for mobility may have implications for the indexing of such studies in electronic databases. To overcome this limitation, electronic indexing synonyms were used for key words to ensure the search was sensitive; however, this may have compromised the precision of the search. A few studies specified a global scale to measure function or disability which may have contained a subsection on gait. For these studies, the reviewer pursued full retrieval in case a breakdown of mobility items was available. The subsection of the BI was reported separately in one study however this was only available six months post-stroke.[87] The main reason for exclusion of the retrieved articles was that the outcome or baseline assessment was conducted out with the timescales specified for this review.

Only including studies that assessed baseline factors within seven days of stroke onset may seem stringent, yet the importance of timing in predictive research cannot be overlooked. Baseline factors shown to be highly predictive within the first two weeks may have different predictive properties if measured at a different timepoint, even a few days has been shown to have an influence on the performance of the model .[53 60] Although the updated search did not identify any further studies, one study did investigate the optimal timing of clinical assessments using an intensive repeated-measures design.[93] Veerbeek et al (2011) concluded that accurate prediction of independent walking at six months is feasible within 72 hours post-stroke using two simple bedside tests; sitting balance and muscle power of the affected leg. Furthermore, recent research has suggested the use of neuroimaging to accompany such clinical assessments to improve the accuracy of predicting motor recovery post-stroke.[94]

An internal validation approach was used here, whereby model performance was tested in the same cohort of patients used to develop the model. There are limitations to this approach in that the generalisability of the model is not challenged; potentially resulting in the model performance being overly

optimistic. It is recommended that performance is best tested in a new cohort of patients as opposed to the original cohort, however, such external validation studies are rare.[70] If predictive models are to become more routinely integrated into clinical practice it is important that the performance of the model is evaluated in a new cohort of patients. The face validity of a predictive tool is important and if it appears to make clinical sense the more likely it will be accepted in clinical practice. For example, some of the factors included in some of the studies identified during the systematic review may not be collected routinely in clinical practice (such as tests of line bisection and constructional apraxia).

Application of predictive models

Being able to predict mobility has important implications for the amount of care needed post-stroke and is of key importance to patients.[49 78] More specifically the ability to ambulate independently is often used as a criterion in determining whether a patient is able to live at home or not.[95] Complications relating to immobility such as chest infections and deep venous thrombosis account for a high proportion (51%) of deaths in the first 30 days post-stroke.[96] Therefore, having knowledge about the patients expected level of mobility may allow planning of preventative measures.

Little is stated in the literature about the real-life implementation of such prediction tools in practice and it would be valuable to establish current levels of understanding and usage by clinicians. The predictive model developed contains factors that can be easily collected in practice therefore increasing its clinical usability. It is acknowledged that algorithms generated from regression models are not always straightforward and accessible for use in clinical practice. Evaluating the cost-effectiveness of predictive models by comparing the resource use and outcomes for one group of patients where the predictive tool was applied with another group where the model was not applied are not usually conducted. This would allow the full impact of predictive tools to be assessed in terms of the cost implications and consequences for the patient and family where accurate or inaccurate information is provided.

As the models have not been fully evaluated they cannot yet be recommended for use in clinical practice. Instead, the models could be used in clinical audit to identify patients whose actual outcome differs from that predicted. Reasons for any differences could be identified to inform patient management or improve the predictive models. The models could be used to stratify patients in rehabilitation trials. This would reduce differences in baseline prediction between the treatment groups. The factors could be used to correct for case-mix in observational studies which would allow patient outcomes from different cohorts (i.e. hospitals) to be compared.

Future direction in predictive research

The use of meta-analysis in predictive research is uncommon due to the availability of evidence for synthesis. In this review this could not be performed largely due to the shortage of comparable predictive studies investigating the same predictors and mobility outcome. Stratifying patients at baseline and reporting the grouped outcomes as seen in some of these studies presents another challenge for reviewers. The diversity of outcome assessments used to evaluate independent walking or return to walking probably reflects the lack of specific walking tools available.[97] The use of individual patient data meta-analysis (IPD MA) may overcome some of these limitations. It is the organisation of multicentre prospective predictive studies adhering to the same protocol collecting the same baseline factors and using the same universally accepted outcome measures which appears to be the favoured approach in this area of research.[98]

The time taken to achieve certain mobility milestones was the primary outcome in three of the included studies.[74 76 78] Proposing timescales for a certain event for different patient types is viewed as useful in goal-setting and as a prompt for further investigation if the patient does not achieve the milestone within the expected timeframe.[78] This focus on time to event is even more problematic for meta-analysis, mainly due to the poor reporting of the hazard ratio and often requires a more complex analytical approach.[98] The time to event is an important clinical question and with a reporting guideline equivalent to the Consolidated Standards of Reporting Trials may overcome this limitation and

facilitate future meta-analysis in this area. The Prognostic Systematic Review Methods Group, part of the Cochrane Collaboration,[99] aims to improve the conduct, analysis and reporting of predictive research. This group should be used as a key reference point for research groups conducting future predictive research in stroke.

2.5 Conclusion

This Chapter includes research that addresses the development stage of the Medical Research Council complex intervention framework. Two new predictive models were developed with some attempt to overcome the limitations highlighted by the systematic review. The models were simple (consisted of a maximum of six factors) and included factors that could easily be collected in routine clinical practice. The models could be used in clinical audit to identify patients whose actual outcome differs from that predicted or be used to stratify patients in rehabilitation trials. The immediate application of these models was to correct for case-mix in the forthcoming observational study (Chapter 3).

3 Establishing baseline physical activity levels in acute stroke patients

3.1 Introduction

Much of today's focus in healthcare is on the delivery of evidence-based practice, reflected by the increased number of audits being conducted. Using relevant process indicators of care and effective monitoring systems, it is important to demonstrate the implementation of evidence-based therapies.

Increasing physical activity levels are a major component in stroke rehabilitation. Physical activity is defined as "any movement of the skeletal muscles of the body that results in energy expenditure."[100] There is suggestion that early intensive activity contributes to the success of stroke unit care and may improve outcomes.[101 102] Studies investigating activity levels of stroke patients indicate that these are low and are the proportion of time that the patient spends in activity is low.[26 46 103-109] Activity levels between patients and stroke units of different countries vary.[107 110] Factors that have been used to explain these differences include patient and stroke characteristics, variations in practice and the rehabilitation environment.[26 111]

There are a number of different methods that can be used to monitor activity in stroke patients such as observational methods and monitoring devices such as an accelerometer (AC).[112] Continuous researcher observation has previously been regarded as the 'gold standard' and previous studies have observed stroke patients in a variety of settings including medical centres,[104] stroke rehabilitation centres[108 109] and ASUs to establish activity levels.[26 46 107]

Researcher observation provides the opportunity to study the environment in which the activity occurred and understand more about the inconsistencies between what people say they do and what actually happens.[113] Limitations with this approach do exist in that it is labour intensive and often includes periods when the patient cannot be observed, i.e. when the patient is in the toilet or moves away outside the observation area. Additionally, the potential bias of a researcher being present also needs to be considered.[46 107] Behavioural

mapping, where time intervals are pre-determined, is an observational sampling method which has been used to establish activity levels in stroke patients and observe objective stroke care processes. Examples of processes which have been observed include the time spent in certain activities, structured therapy and interacting with ward staff and relatives.[107] This method has been used in a number of studies and has proved easy to measure and useful in describing physical activity levels in stroke patients and the environment in which activity occurs.

Accelerometry is the modern day equivalent to researcher observation and is now being proposed as the gold standard. Accelerometers provide a continuous, detailed objective analysis of activity levels and patterns. Accelerometers can be used to collect information about the amount, duration and intensity of upright activity. Uniaxial and triaxial ACs measure the acceleration in a number of directions and quantifies the amount of movement. Although triaxial ACs detect movement in three dimensions, uniaxial ACs are thought to provide more reliable data.[114] The *activ*PAL™ professional (PAL Technologies Ltd, Glasgow, UK) is a monitor worn midline on the anterior aspect of the thigh which has been specifically developed to measure physical activity levels in a range of patients. It is able to discriminate between sitting/lying, stepping and standing allowing time spent in each activity to be measured. The *activ*PAL™ has been used in stroke research.[115] [116] [112] In one study the primary outcome was the number of upright episodes (standing, transferring and walking). It is recognised that quantifying activity by counts does not describe the pattern of activity and may miss important factors such as the time spent in each upright or sedentary episode and the distribution of these events during the day. Information on these factors would provide a fuller picture of the patient's pattern of activity and potentially inform the design and implementation of future rehabilitation interventions.

As well as the amount of physical activity the schedule of activity may also be important i.e. how long should the rest periods be between mobilisation sessions.[3] The impact of lying down for extending periods of time in stroke patients has been previously questioned.[108] Research into sedentary behaviour, which is characterised by prolonged periods of sitting or lying, is growing.[117]

Large epidemiological studies have found a strong association between prolonged periods of sitting each day with negative physiological changes, increased risk of all-cause mortality and cardiovascular-disease.[118] One study has shown that breaking up sedentary behaviour with short bursts of activity significantly reduced cardiovascular disease risk.[119] This has resulted in an emerging interest in how sedentary behaviour is accumulated in stroke.[120]

Activity-based rehabilitation interventions such as VEM aim to improve outcome for patients after stroke. However, to be able to assess the future implementation of effective activity-based interventions in clinical practice, a baseline i.e. what is currently happening with regards to activity needs to be investigated. Therefore, Chapter 3 now presents an observational study which aimed to establish pre-implementation physical activity levels in acute stroke patients. Prior to this study, no observational data for activity levels in acute stroke patients was available for a Scottish healthcare setting. It remains unknown if activity-based rehabilitation interventions do improve outcomes. To further develop the evidence base, the observational data will be used to assess the relationship between activity levels in the acute stages and functional outcome for patients at three and six months, adjusting the analysis for the factors identified to be predictive of outcome (Chapter 2).

Aim

This observational research aimed to quantify upright physical activity level and describe the pattern of upright activity and sedentary behaviour in acute stroke patients using accelerometry, complimented by process information elicited using a standard behavioural mapping technique (BMT).

The objectives of this observational study were as follows:

- To describe the level and pattern of upright physical activity and sedentary behaviour in acute patients in a Scottish healthcare setting using accelerometery and a behavioural mapping technique

- To investigate whether researcher observation can be predicted by accelerometery
- To identify the patient and baseline stroke characteristics which determine levels of upright physical activity using regression analysis
- To investigate whether the level of upright physical activity in the acute stages post-stroke is predictive of functional outcome at three and six months using regression analysis

3.2 Methods

A multicentre observational study design was used to establish the level and pattern of upright physical activity in acute stroke patients. Patients were recruited from three ASUs in the West of Scotland. Activity monitoring using researcher observation and accelerometry was conducted for each recruited patient, in the ASU for nine hours on one day between Monday to Friday. The BI was administered at three and six months by telephone interview.

Patients over 18 years of age with a clinical diagnosis of first or recurring stroke admitted to an ASU with either a haemorrhage or infarct within the first 14 days of stroke onset were approached for inclusion. Only patients who, at the time of recruitment, were not planned for discharge were approached. All patients or their nearest relative provided informed written consent prior to enrolment. Patients were excluded if they had already been recruited to another rehabilitation intervention study as this may have influenced standard mobility practices. Patients for palliative care were excluded.

Recruitment strategy

The research nurses were informed of the study details and the inclusion/exclusion criteria. Oral presentations were provided locally; at hospital stroke research meeting groups and Managed Clinical Network Research and Development meeting groups to raise the profile of the research. The Scottish Research Network (SRN) nurse acted as the key contact for each of the hospital sites.

Contact was made daily with the research nurses in order to receive updates on new patients admitted to the ASUs and to assess their suitability for recruitment. All potential study patients were screened and if eligible, the patient or nearest relative was approached and provided with the study patient/relative information sheet (Appendix 7) 24 hours in advance of any decision to participate being made. Potential participants and/or the nearest relative were also provided with verbal information about the study. The patient, where able, completed the consent form (Appendix 8). Where a patient was unable to complete the consent form fully and/or eligibly, a witness was sought to overview the recruitment process and verify the patient's verbal consent. The SRN research nurses recruited patients when the researcher was unable to do so.

3.2.1 Accelerometry

The type of AC used was the *activ*PAL™ professional (PAL Technologies, Glasgow, UK). The main features of the *activ*PAL™ are that it is uniaxial, lightweight (weighs only 15mg), is slimline (only 7mm thick) and can collect and store data continuously for up to seven days. The *activ*PAL™ was used to monitor physical activity between 08:00 and 17:00 for each recruited patient (to align with the monitoring timeframe used in the BMT protocol). The *activ*PAL™ monitor was securely positioned onto the anterior aspect of the patient's thigh using a PAL*stickie* (double-sided hydrogel adhesive pad) at the start of monitoring. For hemiplegic patients there is some suggestion that ACs can be placed on either the non paretic or paretic side.[121] To ensure consistency in this study the monitor was fixed to the patient's unaffected thigh. The monitor was removed in the event of washing, bathing or showering or if the patient was attending a Magnetic Resonance Imaging (MRI). The time of monitor removal and re-attachment was noted. The *activ*PAL™ has been shown to be a valid and reliable device for measuring step number and cadence in a healthy adult population [122-124] and in patients with problems such as chronic low back pain.[125] A recent review suggests that ACs can produce valid and reliable data about the physical activity of patients with stroke.[126]

3.2.2 Researcher observation

Intermittent researcher observation was conducted for each recruited patient between 08:00 and 17:00 in the ASU between Monday to Friday. The researcher employed a well-established BMT;[127] to enable comparability of results with other studies. This technique involved structured observations, of approximately one minute duration, at 10 minute intervals throughout the day with four, 10 minute, rest breaks scheduled. The monitoring timeframe adopted in previous studies has varied from one day to five days.[128]

The BMT is designed to be unobtrusive, using distance observation where possible, and does not intrude on patients behind closed doors or curtains. Patients may become aware of the observer, but in this population it is unlikely that they will alter their behaviour in response to observation since many people newly diagnosed with stroke require physical assistance to move.

The BMT procedure used was designed to provide a snapshot of routine activity of acute stroke patients. Due to the short length of patient stay in the ASUs the use of a longer monitoring timeframe observation period was considered impractical. Training in mapping procedure was provided by the author of the protocol.[127] The type of motor activity, patient location and the people present were recorded on a paper case report form (CRF) at each time interval. Ten motor activity, 14 person present and five locations categories (bathroom, bedroom, hall, therapy area or off ward) were used (Table 3-1). Patient's privacy was respected and activity behind closed curtains was not observed and patients were not followed off the ward. In such instances, information from periods where the patient could not be observed was determined by asking the patient or staff member as soon as they became available again and was noted as unobserved if unobtainable.

Table 3-1 Motor activity and person present classifications

Motor activity	Person present
No active motor (supine or side-lying)	Alone
Sit support in bed	Medic
Sit support out of bed	Nurse 1
Hoist transfer	Nurse 2
Roll and sit up	Nursing assistant 1
Sit no support	Nursing assistant 2
Transfer feet on floor	Physiotherapist
Stand	Occupational therapist
Walk	Speech and language therapist
Stairs	Family
	Patient transport
	Interpreter
	Other members of multidisciplinary team
	Other

3.2.3 Data collection, processing and storage

Information on patient demographics, stroke characteristics and the time of first mobilisation were collected prospectively from patient case notes. The findings from the systematic review and predictive modelling presented in Chapter 2 informed the baseline factors that should be collected. The National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) assessments were conducted on the day before the observation or on the day of observation. Other baseline factors included level of consciousness; muscle power and gait (all using the sub-section of the SSS) were recorded. The treating physiotherapist assessed the patient's functional mobility using the Mobility Scale for Acute Stroke (MSAS) on the day before the observation (+/- one day). Patients were followed up using the BI at three month and six months by telephone interview. Telephone assessment of function with the BI has been shown to be a reliable in comparison to a direct face-to-face assessment.[129]

Contact information was collected from the patient, nearest relative or case notes for the purposes of follow-up. This contact information was kept separately from the CRFs and was treated as highly confidential in a locked area in an office at all times. On discharge, the patient's general practitioner was advised in writing of the patient's involvement in the study. The researcher contacted the person who provided consent for involvement to the study to arrange a convenient time to conduct the three month follow-up telephone interview. Patients recruited to the study were provided with a unique identification number (ID) which was used when completing the CRFs.

Completed observed motor activity CRFs were submitted via fax within one week of completion of the day of observation to a specialist centre in Melbourne for processing. The CRFs did not contain any patient identifiable information. The CRFs were converted and saved as a digital image using Teleform™ software, checked visually and uploaded to a database. The data underwent computer logic testing with data queries being sent via email by the centre's administrator. The database was transferred electronically on completion of patient recruitment. Data from the *activ*PAL™ monitors were downloaded to a password secured computer using the software package (*activ*PAL™ Professional Research Edition, version 5.8.50). The CRF folder was stored locally in a locked cabinet and office. Data from baseline CRFs were inputted into a database on the day after monitoring. The CRFs containing the patients contact details were held in a separate folder and locked cabinet. Paper based data will be stored until June 2016, five years from study completion.

3.2.4 Ethics and management approval

The study was granted ethical approval from Scotland A Research Ethics Committee on 22nd July, 2010 and subsequent requests for management approval were granted by NHS Greater Glasgow and Clyde Research and Development on 6th September, 2010 and NHS Lanarkshire Research and Development on 1st October, 2010. To allow access to the study sites honorary contracts with each of the health boards were applied for and granted on 1st October, 2010 and 29th November, 2010. An audit of this study was conducted by the sponsor, NHS Greater Glasgow and Clyde Research and Development, on 4th January, 2012.

3.3 Statistical analysis

3.3.1 Sample size

The sample size calculation was based on a previous study which estimated time spent upright as measured by an AC as 8.3% (SD 8.5).[112] The recruitment of 60 patients was considered feasible and representative. The literature estimates (mean and standard deviation [SD]) showed that this sample size would provide an acceptable level of precision (95% confidence interval [CI], 6.1 to 10.5). The sample size was inflated by 10% to account for patient drop out or technology

failure resulting in loss of data. Therefore, the study aimed to recruit 66 patients, a sample size considered clinically representative and feasible in relation to the study's recruitment timeframe. Confidence intervals were calculated using CI Analysis software.

3.3.2 Data management

For the AC data the software package *activ*PAL™ Professional Research Edition was used initially, to provide chart summaries of total time spent in sitting/lying (defined as sedentary behaviour), standing and walking (together defined as upright activity) for each patient. The charts were cross-checked with the BMT data to identify any periods that were known to be out of character for that patient (large amounts of stepping activity) or ward practices (such as high dependency patients having brief upright activity in the first hour of monitoring). As part of the *activ*PAL™ Professional Research Edition package an Excel file was downloaded which provided summaries of total time spent in each activity classification for each hour as well as providing the time spent in sit/lying, standing and stepping every 15 seconds. For a more in-depth analysis the *activ*PAL™ files generated by the *activ*PAL™ Professional Research Edition software were imported into the Health and Social Care (HSC) PAL analysis software which has been developed by Professor Malcolm Granat's research team at the School of Health and Social Care, Glasgow Caledonian University. This software provides more detailed data and allows time periods to be selected for individual patients. Individual patient activity data were extracted for the monitoring time excluding time points when it was known that the monitor had been removed (for the purpose of showering or MRI) or momentarily detached from the patient's thigh. The more detailed data includes the number of upright, standing, walking, transitions and stepping events (Appendix 9 for full definitions). The BMT data were provided by the processing centre in an Excel spreadsheet. The data were manipulated in Excel to reformat prior to being transferred into the statistical software package for cleaning and analysis.

3.3.3 Data analysis

Activity data (AC)

The primary outcome was the proportion of time spent upright as measured by the AC. For each patient the amount of time spent upright as a proportion of the total recording time was calculated. The total upright time for each patient for each hour of the monitoring period was calculated with the group data for each hour reported as the median time. Additionally, the total upright time (sum of standing and stepping time) and total sedentary time was calculated for every hour of the monitoring period. Time did not have a normal distribution, therefore group data for each hour were summarised as medians with the 25th and 75th percentiles (interquartile range [IQR]) reported. The HSC PAL software provides the time at which a change in output category (i.e. a transition from sitting to standing) occurs and also the duration of each event (defined as continuous periods of one activity). This information was used to investigate the accumulation of events throughout the day. Each event was classified into one of the following time intervals which have been used previously (≤ 5 minutes, > 5 to ≤ 10 minutes, > 10 to ≤ 30 minutes, >30 to ≤ 60 minutes, > 60 minutes).[130] The amount of time spent in each of the time intervals as a proportion of total time spent upright/sedentary was calculated.

This required decisions to be made regarding the appropriate extraction of data. In particular, whether or not to include events that crossed imposed start and end times. The HSC software is programmed to include the first event that crossed the start time so this may mean crediting a patient with a five minute duration event, when in fact it was 125 minutes long. Some researchers enforce rules (personal communication, 2011) that if the proportion of the overlapping event is more than 50% out with the monitoring time then it should be excluded. Whether or not to apply such a rule to these data was assessed by investigating the output for individual patients. Considering this potential underestimation it was decided that these events should be included. An example of an AC output is provided in Appendix 10. The same consideration was given to events that overlapped times when the monitor was removed or reattached. Again, using this case by case assessment approach the end of the event (monitor off) usually

inferred the beginning of a new event such as a transition from sedentary to upright in preparation for washing or a MRI scan, therefore events that overlapped were included. Subgroup analysis using categories of stroke severity measured on the day of observation (mild stroke: NIHSS ≤ 7; moderate and severe stroke: NIHSS ≥ 8) was conducted to investigate the association between severity and the activity outcome measures. The number of patients with severe stroke (NIHSS >16) was too low (n = 5) to justify separate analysis. The NIHSS score that was extracted from medical notes on admission was used where the NIHSS had not been assessed on the day of monitoring.

Other activity-related data (BMT)

The *activ*PAL™ does not detect between lying and sitting so the BMT data were used to provide information of these types of sedentary behaviour. For example, a patient shown to have been consistently sedentary all day may have actually been hoisted from bed to chair. The *activ*PAL™ would have missed this important information. For the BMT data, the total number of observations for each type of motor activity was calculated. As more than one activity may have been observed in one observation period the highest level of activity obtained in each of the observations was used. The motor activity categories were classified, again, into upright activity or sedentary behaviour. Sedentary behaviour was further classified as in-bed or out-of-bed (Table 3-2).

Table 3-2 Classifications of motor activity categories from BMT

Motor activity	Type of behaviour
No active motor (supine or side-lying) Sit support in bed	Sedentary (in-bed)
Sit support out of bed Hoist transfer Sit no support	Sedentary (out-of-bed)
Transfer feet on floor Stand Walk Stairs	Upright activity

To investigate relationships between upright activity and person present or location data from the BMT and AC were synchronised and combined. Firstly, to

summarise the person present data, the groups were collapsed into eight categories (Table 3-3) and the total number of observations was calculated for each person present and location categories.

Table 3-3 Classifications of person present categories from BMT

Original 'person present' category	New 'person present' category
Alone	Alone
Medic	Medic
Nurse 1 Nurse 2 Nursing assistant 1 Nursing assistant 2	Nurse
Physiotherapist Occupational therapist	Therapist
Speech and language therapist	Speech and language therapist
Family	Family
Patient transport	Patient transport
Interpreter Other MD team Other	Other*

* The 'other' category included 'other MDT staff' (pharmacists and dieticians), other hospital staff (phlebotomists, smoking cessation representatives, cleaning or catering staff) other patients or talking on mobile phone.

Secondly, appropriate summary estimates for each time point were calculated. The amount of time spent upright as a proportion of the total recording time in each 10 minute time interval (i.e. 08:00 to 08:10) was calculated for each patient. This was summarised as the mean proportion of time spent upright. For each 10 minute time interval (08:00, 08:10 etc) the total number of nurses and therapists present as a proportion of the total number of observations was calculated. Likewise, the total number of patients observed in each location category as a proportion of the total number of observations was calculated. This required the assumption that the person present and location remained the same for each 10 minute interval.

Different methods to monitor activity

In order to assess the agreement between AC and BMT two comparable units of measurement were identified and calculated for each method. For the AC data the time spent upright in seconds as a proportion of the total monitoring time for each one minute time interval i.e. 08:00 to 08:01, 08:10 to 08:11 was

calculated. This was summarised as the mean proportion of time spent upright for each time interval and enabled the AC data to be time-matched with the BMT data. For the BMT data the number of times upright as a proportion of the total number of observations i.e. 08:00 to 08:01, 08:10 to 08:11 was calculated. These proportions were plotted against each other. Linear regression analysis was used to quantify the extent researcher observation can be predicted by accelerometry.

Predictors of upright physical activity levels

Multivariate linear regression was used to assess which baseline characteristics were significantly ($p \leq 0.05$) predictive of upright physical activity. A logarithmic transformation was applied to the dependent variable, time spent upright. The variables that were entered into the regression model were as follows: stroke severity (NIHSS baseline), mobility (MSAS score), time in hours from stroke onset, previous stroke and family present (total number of times family were present as a proportion of the total number of observations for each patient).[46]

Upright physical activity as a predictor of functional outcome

Univariate analysis was undertaken to examine the association between potentially predictive baseline characteristics and functional outcome at three and six months. The factors identified as predictive of mobility at 30 days (refer to Chapter 2) were used here. These were as follows: age, stroke type (OCSP classification, coded as TACS = 1, no TACS = 0), living alone (coded as alone = 1, not alone = 0), level of disability (mRS $\geq$ 3 coded as high disability = 1, mRS < 2 coded as 0), level of function (BI < 17, coded as dependent = 1, BI $\geq$ 18 coded as 0) and stroke severity (NIHSS $\leq$ 7, coded as mild stroke = 0, NIHSS $\geq$ 8 coded as moderate and severe stroke). Patient scores from the BI were dichotomised to create a binary outcome (BI $\geq$ 18 coded as independent = 1 or not independent = BI < 17). The variables that were statistically significant ($p < 0.1$) on univariate analysis were included in the multivariate model.[72] Logistic regression was employed, using backward stepwise regression to drop the least significant variables ($p < 0.1$), to identify the variables which best predict function.

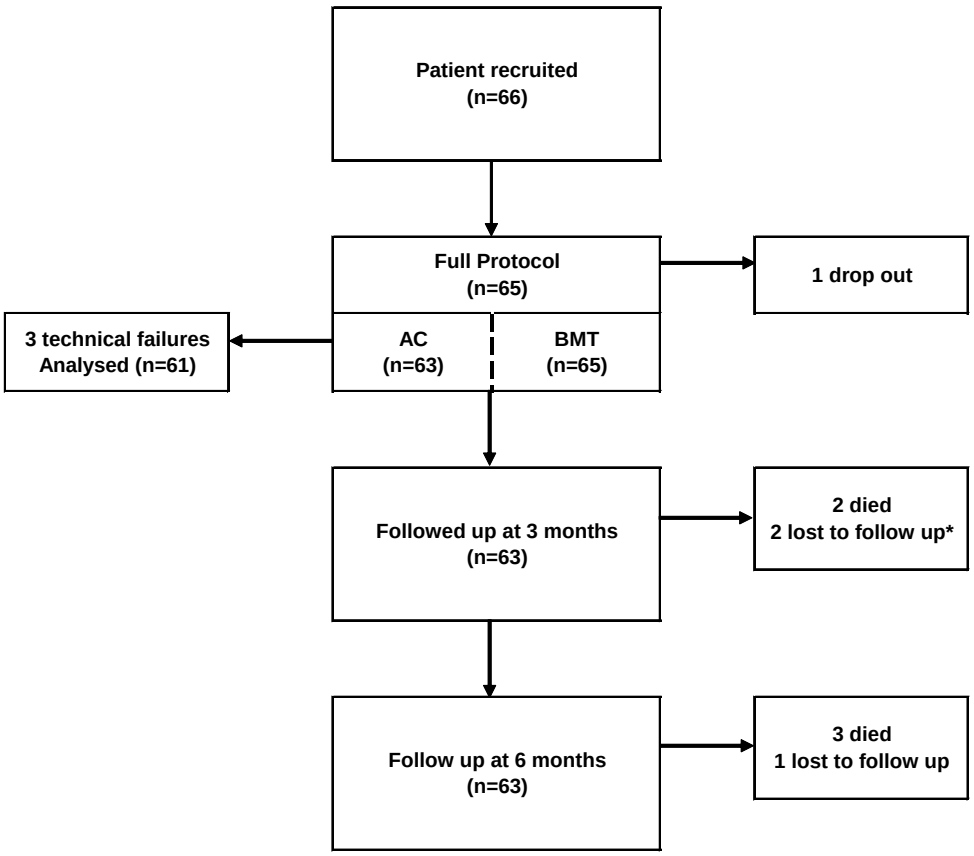
3.4 Results

3.4.1 Stroke unit and patient characteristics

The number of beds in the ASUs at each of the hospitals was 14 (hospital A), 18 (hospital B) and 19 (hospital C) and the average length of stay based on local audits ranged from between seven to 14 days. Due to the re-design of stroke services in the local area, the stroke unit at hospital B expanded from one ward to two wards with a total of 37 beds. Staffing levels were in adherence with SIGN guidelines.[2] Two hospitals delivered thrombolysis with each of the hospitals having a dedicated area and one additional bed prioritised for thrombolysed patients. The layout of the wards varied with a mixture of single rooms, four-bedded rooms and open bays. Hospital A had five single rooms, hospital B had two and hospital C had three. Therapy rooms were present on the ward for two of the hospitals while for the hospital C it was off-ward but in close proximity to the stroke unit. There was a patient lounge, containing a television and chairs in one hospital and a dedicated relative's room in another.

Sixty-six patients were recruited between October 2010 and June 2011. Twenty-nine patients were recruited from hospital A, 26 from hospital B and 11 from hospital C. Consent was withdrawn by the relatives of one patient on the day of monitoring as the patient experienced neurological deterioration. Eight patients were discharged or transferred on the day of monitoring having completed between 37.8% and 90.7% of the total monitoring time. The data from these patients were included in the analysis. Discharge from physiotherapy and mobility function were factors considered to be associated both with hospital discharge and activity levels. When investigated no significant differences were detected for the factors (discharge from physiotherapy and mobility function) between the patients that had been discharged and those that had not been discharged ($p = 0.72$ and $p = 0.42$, respectively). Overall, five patients died, two patients were non contactable for at least one of the follow-up phone calls and one patient was lost at follow-up and therefore had no outcome data (Figure 3-1).

Figure 3-1 Study recruitment flowchart



*** Patient later followed up at 6 months**

3.4.2 Patient demographics

The demographics of the 66 patients recruited from the three hospitals are shown in Table 3-4. The mean age of patients was 73.2 years (SD 9.8) and proportions of males and females were similar. The majority of patients were previously independent (56.1%), with 19.7% of patients having a history of atrial fibrillation and about 15% of patients having had a previous stroke. The median NIHSS score on admission was 5 (IQR 3 to 10) which reduced to 3 (IQR 2 to 5) on the day of observation. The median time from stroke onset to the day of observation was 5.5 days (IQR 4 to 9). The median NIHSS score of the 12 patients that received thrombolysis was 15 (IQR 6.5 to 19.0) on admission and 5 (IQR 3 to 17) on the day of monitoring. Five patients had a haemorrhage. Two patients who had a clinical diagnosis of stroke at the time of recruitment were later confirmed negative for stroke. These patients remained in the analysis. At follow-up a further patient had subsequently been diagnosed with Guillain-Barre

syndrome, opposing the initial stroke diagnosis. The patient was being treated as per stroke protocol and under the care of the stroke unit during the day of observation so was included in the analysis.

All patients had been either mobilised up to sit out of bed or stand/walk prior to monitoring. The first time to mobilisation was extracted from case notes for 21 patients. This was not available for the remainder of patients. The median time from stroke onset to first mobilisation in these patients was 37.5 hours (IQR 26.5 to 50.0) and the time from hospital admission to first mobilisation was 26.0 hours (IQR 19.5 to 40.3). The first mobilisation was provided by two physiotherapists in the majority of occasions (51.5%) and one physiotherapist (36.4%), two nurses (10.6%) or one nurse (1.5%) for the remainder. Over a quarter of patients were independently mobile of which 75% were able to walk greater than five metres. Just over 10% of patients not able to mobilise independently were classified as 'bedridden/wheelchair' bound by the gait sub-section of the SSS. Two patients with stroke also had dementia and three patients were considered to be agitated (stroke cause).

Table 3-4 Baseline demographics and clinical factors

Factor	All patients (n=66)
Age (mean, SD)	73.2 (9.8)
Female	28(42.2%)
Living alone	25 (37.8%)
Previous stroke	9(13.6%)
Pre-morbid disability (mRS)	
0 - No symptoms at all	48 (72.7%)
1 - No significant disability	13(19.7%)
2 - Slight disability	3(4.6%)
3 - Moderate disability	2(3.0%)
Stroke risk factors	
history of atrial fibrillation	13 (19.7%)
Stroke severity (NIHSS)	
on admission (median, IQR)	5 (3-10)
mild category	45(68.2%)
moderate/severe category	21(31.8%)
Day of monitoring (median, IQR)*	3 (2-5)
mild category	52(78.8%)
moderate/severe category	14(21.2%)
Stroke type (OCSP)	
LACS	19(28.8%)
PACS	17(25.8%)
POCS	11(16.7%)
TACS	12(18.2%)
Haemorrhage	5(7.6%)
Uncertain	2(3.0%)
Thrombolysis administered	12 (18.2%)
Level of disability (mRS)	
0 - No symptoms at all	2(3.0%)
1 - No significant disability	3(4.6%)
2 - Slight disability	12(18.2%)
3 - Moderate disability	19(28.8%)
4 - Moderate to severe disability	24(36.4%)
5 - Severe disability	6(9.1%)
Conscious (SSS)	66(100.0%)
Normal leg strength(SSS)	25(37.9%)
Function (BI) (median, IQR)	60(30-85)
Mobility function (MSAS)	27(19-29)
Independently mobile (mRS)	17(25.8%)
Days from stroke onset to day of monitoring (median, IQR)	5.5 (4-9)

Entries are numbers (percentages), unless stated otherwise.

*Based on 53 patients

mRS: Modified Rankin Scale; NIHSS: National Institute Health Stroke Scale; OCSP: Oxford Community Stroke Project Classification; LACS: Lacunar Circulation Syndrome; PACS: Partial Anterior Circulation Syndrome; POCS: Posterior Circulation Syndrome; TACS: Total Anterior Circulation Syndrome: SSS; Scandinavian Stroke Scale: BI; Barthel Index: MSAS; Mobility Scale for Acute Stroke

Details of accelerometer data

The total amount of excluded data was 5.1%. Eight patients were discharged or transferred on the day of monitoring which resulted in 30.4% missing data of the total possible recording time (72 hours). For the remaining 57 patients 513 hours

of monitoring was accumulated. Technical failure was the reason for excluding the majority of data from these 57 patients. Technical failures included a battery light turning on resulting in the monitor being removed and replaced by another, an electronic component failure and the monitor being fixed on upside down by staff member. This resulted in 18.7 hrs (73.3% of total missing) of data being excluded. As a result of technical failure two patients had no activity data, therefore including the patient that withdrew three patients in total had no AC data (Figure 3-6). In comparison, the proportion of data missing because the device had been taken off for showering, attending a MRI or due to inadvertent detachment was much lower (Table 3-5). The monitor detached briefly in one 'agitated' patient and one patient with dementia required an additional explanation before re-attaching after a shower. One patient asked for the monitor to be removed 54 minutes prior to the monitoring end time which was done.

Table 3-5 Reasons for excluded accelerometer data

Reason for excluded data	No of events*	Total time(hrs)
Monitor accidently detached	3	0.4 (1.5%)
Monitor deliberately removed**	12	7.4 (27.8%)
Technical failure	4	18.7 (70.8%)
Total excluded time	19	26.5 (5.1%)
Total possible recording time		517

* Based on 18 patients

** For purposes of MRI/showering/patient preference

Details of behavioural mapping data

The potential number of BMT observations was 3,479 less 249 (7.0%) when the observer had a break. Twenty-five observations (0.8%) did not have information collected for any of the BMT items. Reasons for this missing information were that the patient was off ward for medical tests or the patient was not observable i.e. they were behind closed curtains, in therapy rooms or in the bathroom and the information was not obtained retrospectively. The majority of observations were conducted at hospitals A and B (Table 3-6).

Table 3-6 Researcher observations conducted by hospital site

Hospital ID	Number of patients	Number of observations	Not observed*
A	29	1274 (42.6%)	189 (38.7%)
B	26	1178 (39.4%)	234 (47.9%)
C	11	538 (18.0%)	66 (13.5%)
	Total	2990 (100%)	489 (100%)

* Patient not observed or researcher on break

3.4.3 Activity outcomes

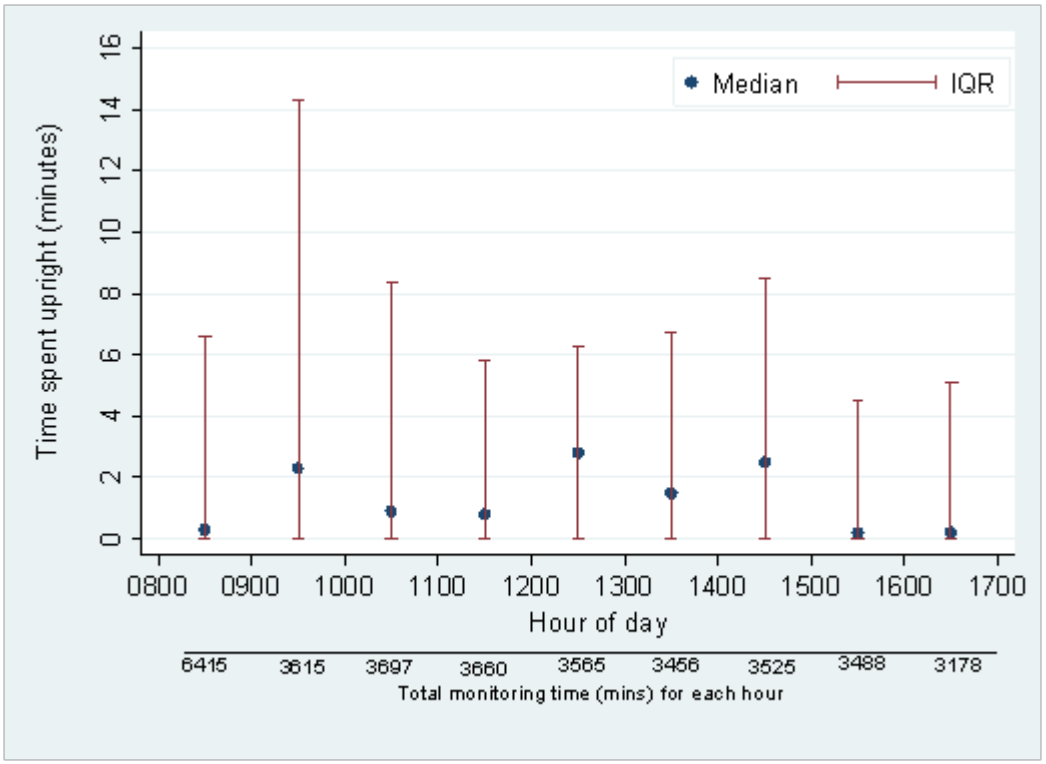
Both the AC and BMT data were used in this section. Activity recorded using BMT is described in percentages of the observed nine hour day. Activity recorded with AC is described in minutes, events, steps or transitions over the same nine hour day. Patients spent a mean proportion of 8.2% (95% CI, 6.2 to 10.1) time in upright activity with an average standing time of 6.8% (95% CI, 5.2 to 8.5) and an average walking time of 1.3% (95% CI, 0.9 to 1.7). The proportion of time spent sedentary was 91.8% (95% CI, 89.9 to 93.8). The median time (minutes) spent upright was 31.91 minutes (IQR 11.20 to 59.85) and the median time spent sedentary was 491.41 minutes (IQR 436.68 to 526.55) over a nine hour day. There was variation between patients in the amount of time spent upright, three patients (one patient remained in bed, two patients were transferred up-to-sit) spent zero time upright, while one patient spent 34.3% of the time upright. Table 3-7 provides the time spent in each of these activities as well as the number of upright and sedentary events.

Table 3-7 Summary of activity measure (AC data)

Activity measure (time, minutes)	Median (n=63)	IQR
Upright time	31.91	11.20-59.85
Standing time	25.89	10.90-46.0
Walking time	2.96	0.22-10.32
Sedentary time	491.41	436.68-526.55
Number standing events	32.00	8.0-70.0
Number of walking events	17.00	1.0-49.0
Number of sedentary events	12.00	7.0-25.0
Number of transitions	24.00	14.0-51.0
Number of steps	140.00	8.0-684.0

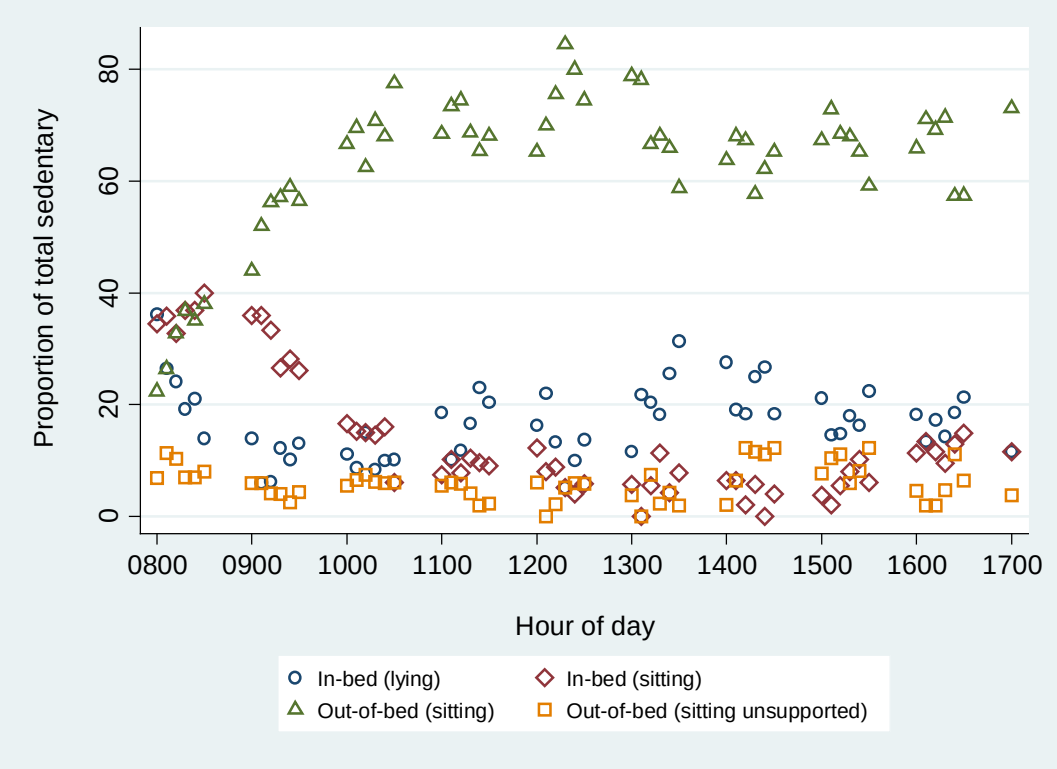
The pattern of time spent upright during the observational period is shown in Figure 3-2. Median time spent upright was at its highest at 09:00 and 12:00 (2.30 minutes [IQR 0 to 14.30] and 2.80 minutes [IQR 0 to 6.30], respectively) and lowest at 15:00 and 16:00 (0.2 minutes [IQR 0 to 5.6 and 0 to 4.5 minutes, respectively]). The pattern of time spent sedentary shows the inverse pattern to upright activity with sedentary behaviour reduced at 09:00, 12:00 and 14:00. The largest amount of variation in time spent upright and in sedentary behaviour between patients occurred at 09:00 with time spent upright ranging from between zero minutes to 34.0 minutes upright. The pattern of upright activity and sedentary behaviour reflects the typical day of a patient in stroke unit care. At 09:00 patients are getting up out of bed and engaging in washing and dressing, at 10:00 to 11:00 they are sitting out of bed in a chair, at 12:00 moving about in preparation for lunch and at 13:00 return to bed after lunch. The peak at 14:00 reflects therapy time or patients getting back up to sit in preparation of family visiting (ranging from 14:30 to 16:00). The median time to the first upright event from 08:00 was 45.56 minutes (IQR 5.63 to 142.08).

Figure 3-2 Median time spent upright by hour of day (AC data)



The BMT data revealed that the majority of time spent sedentary can be explained by patients sitting out-of-bed as opposed to in-bed (70.7% versus 29.3%) Approximately the same amount of time was spent lying in bed as sitting in-bed (15.2% versus 14.1%). At most hours of the day, the majority of observations are of patients up sitting in a chair indicating that patients are spending prolonged periods in sitting. The level of out-of-bed behaviour was highest at 12:00 which was then reduced by 13:00, explained by patients returning to bed early in the afternoon (Figure 3-3).

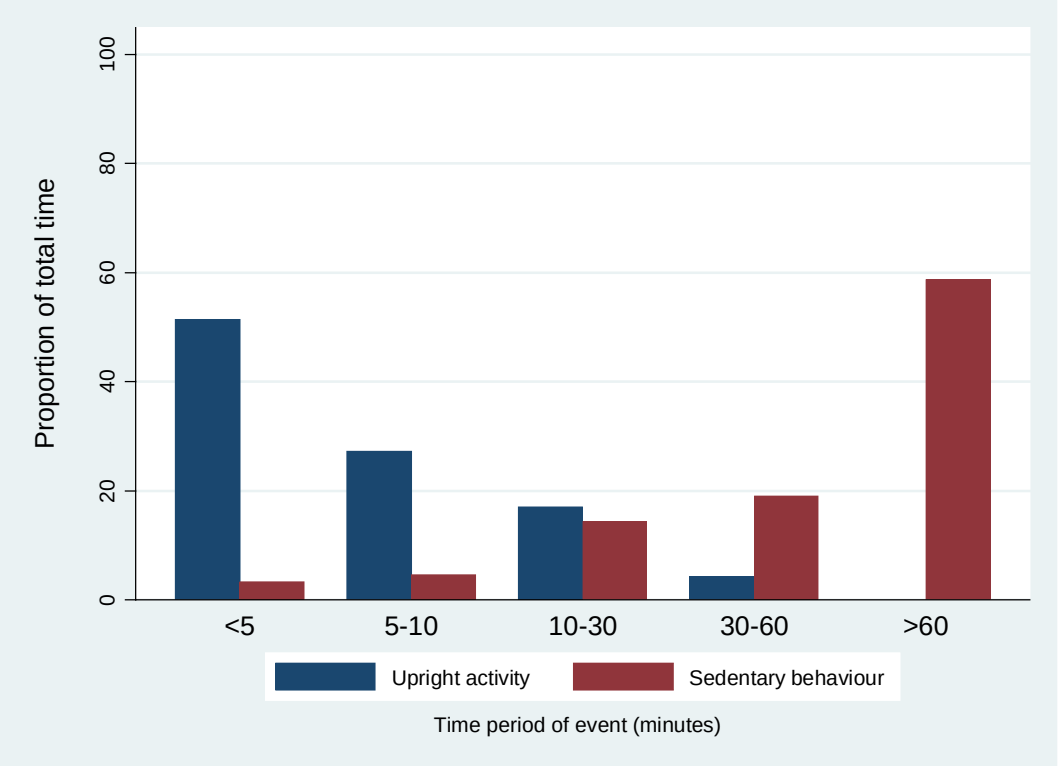
Figure 3-3 Pattern of sedentary behaviour by hour of day (BMT data)



When investigating how upright activity and sedentary behaviour were accumulated the greatest proportion (51.4%) of time spent upright was spent in epochs less than 5 minutes. The time spent upright in each epoch is as follows: > 5 to ≤10 minutes; 27.2%, > 10 to ≤ 30 minutes; 17.0%, > 30 to ≤ 60 minutes; 4.3%. No upright time was accumulated in epochs of > 60 minutes. A reverse pattern was observed for sedentary events whereby the majority (58.7%) of

sedentary time was accumulated by prolonged episodes of greater than 60 minutes. The time spent sedentary in each epoch is as follows: ≤ 5 minutes; 3.3%, > 5 to ≤ 10 minutes; 4.6%, > 10 to ≤ 30 minutes; 14.4%, > 30 to ≤ 60 minutes; 19.0% (Figure 3-4). The majority of total sedentary time was accumulated by prolonged episodes of > 60 minutes sedentary behaviour. The U-shaped pattern of accumulating upright and sedentary behaviour can be explained by the increasing amounts of time spent upright as the length of each time category increased.

Figure 3-4 Total time upright and sedentary by length of event (AC data)



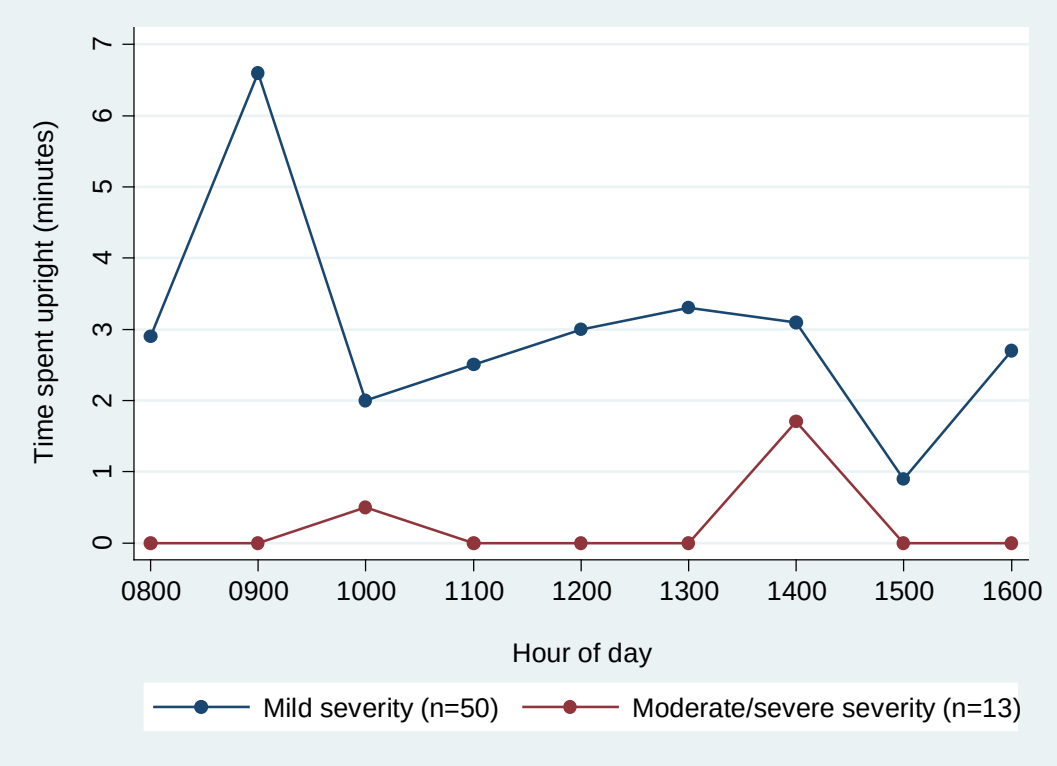
3.4.4 Activity outcomes by severity

Both the BMT data and the AC data were used in this section. There were 52 patients in the mild stroke group and 13 in the moderate/severe stroke group (excludes the patient that dropped out). The mean proportion of time spent upright over the day for patients with mild stroke was 9.8% compared to 2.1% for patients with moderate/severe stroke. The proportion of time spent standing was higher than walking for both mild and moderate/severe groups (8.2% versus

1.6% compared to 1.9% versus 0.2%). Patients with mild stroke spent 43.49 minutes upright (IQR 13.24 to 76.83) and patients with moderate/severe stroke spent 9.50 minutes upright (IQR 1.76 to 15.59). Patients with mild stroke spent 464.77 minutes sedentary (IQR 436.65 to 507.15) and patients with moderate/severe stroke spent 528.36 minutes sedentary (IQR 514.58 to 537.55).

The median time spent upright for each hour by stroke severity is shown in Figure 3-5. Once again, upright activity was much lower in the moderate/severe stroke patients. Not only did the amount of time differ, pattern of activity also differed between groups. The pattern of upright activity differed between the two severity groups. The median time spent upright peaked in the morning for both groups, earlier for patients with mild stroke. Patients with mild stroke had a reduction in upright time from 14:00 while at the same time, peaked from patients with moderate/severe stroke. This was likely to be associated with patients being mobilised during therapy, returning to bed or getting up to sit for visiting. Minimal upright activity occurred between 11:00 and 13:00 for moderate/severe patients and was lowest at 15:00 for patients with mild stroke (median 0.9 minutes [IQR 0.0 to 6.95]). Patients with moderate/severe stroke took longer to commence upright activity than patients with mild stroke. The median time to the first upright event from 08:00 was 35.22 minutes (IQR 3.75 to 85.25) for patients with mild stroke and 149.39 minutes (IQR 98.67 to 177.57) for patients with moderate/severe stroke.

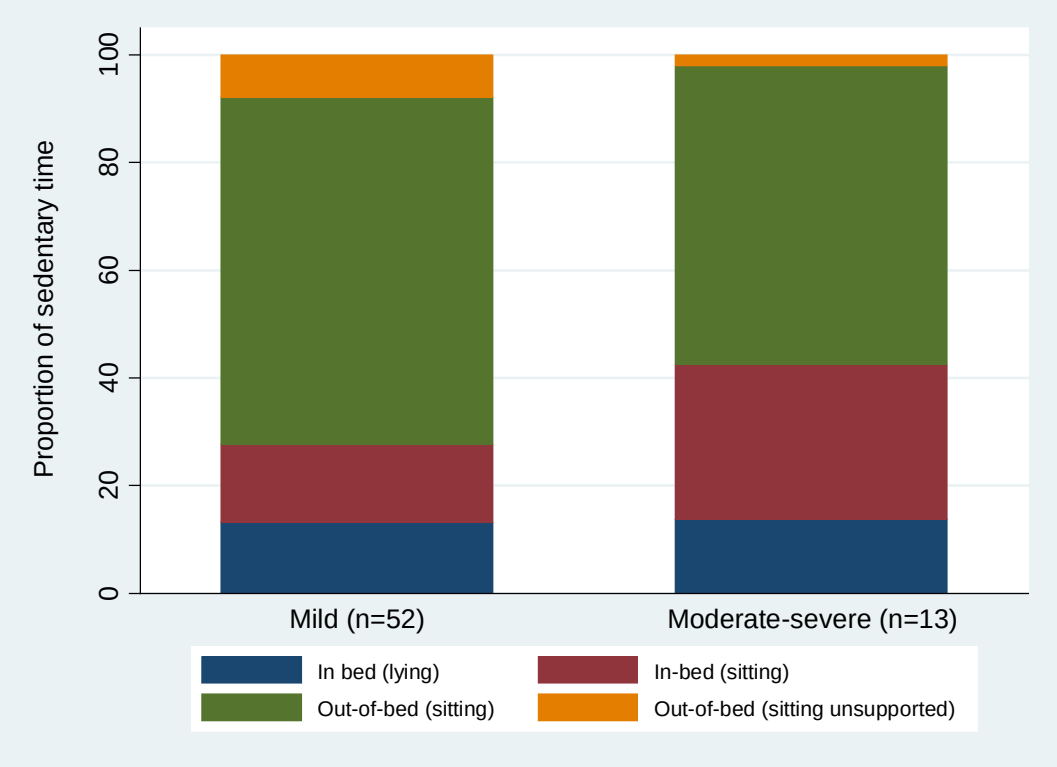
Figure 3-5 Median time spent upright over time by stroke severity (AC data)



Mild stroke = NIHSS ≤ 7, Moderate/severe stroke = NIHSS ≥ 8. The number of patients in the mild stroke category is 50 as AC data was not available for two patients with mild stroke.

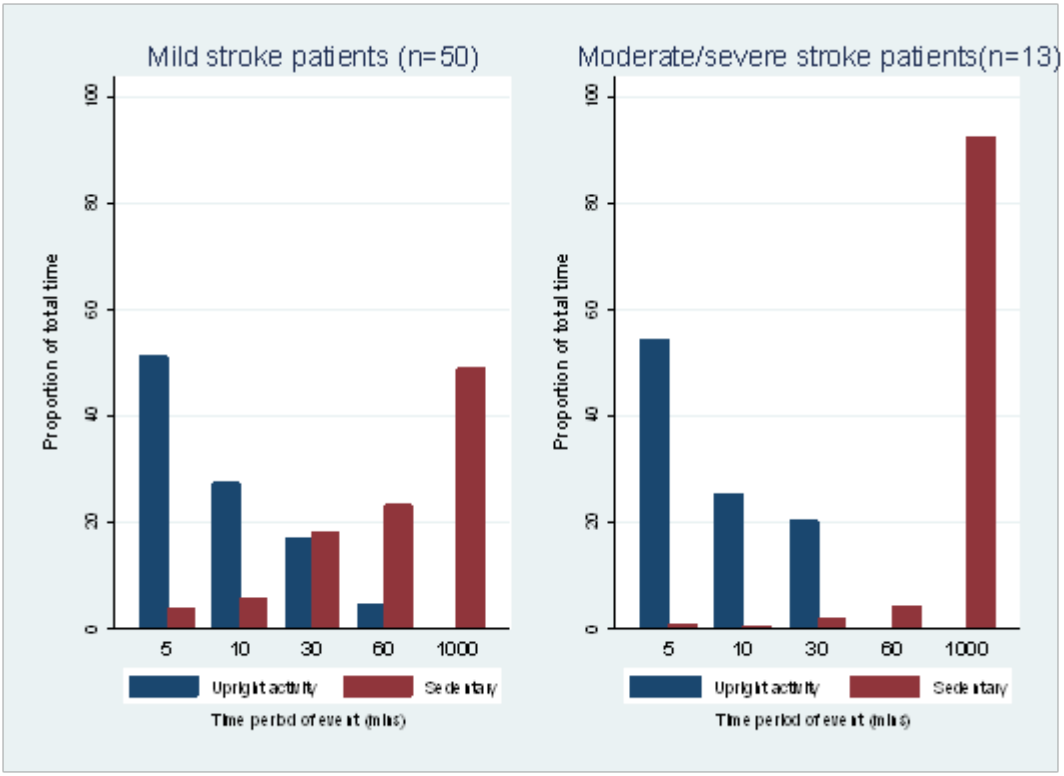
Patient in both severity groups spent similar amounts of sedentary time in-bed (12.0% and 13.5%, respectively) and the highest proportion of time out-of-bed sitting (58.6% and 53.0% respectively) (Figure 3-6).

Figure 3-6 Type of sedentary behaviour by stroke severity (BMT data)



For both groups most upright activity was accumulated in epochs of ≤ 5 minutes (mild = 51.1%, moderate/severe = 54.5%) (Figure 3-7). There were differences in how sedentary behaviour was distributed between the groups. For patients with moderate/severe stroke a higher proportion of sedentary behaviour was accumulated in epochs of > 60 minutes (92.5%) compared to patients with mild stroke (49.0%).

Figure 3-7 Time upright/sedentary by length of event and severity (AC data)



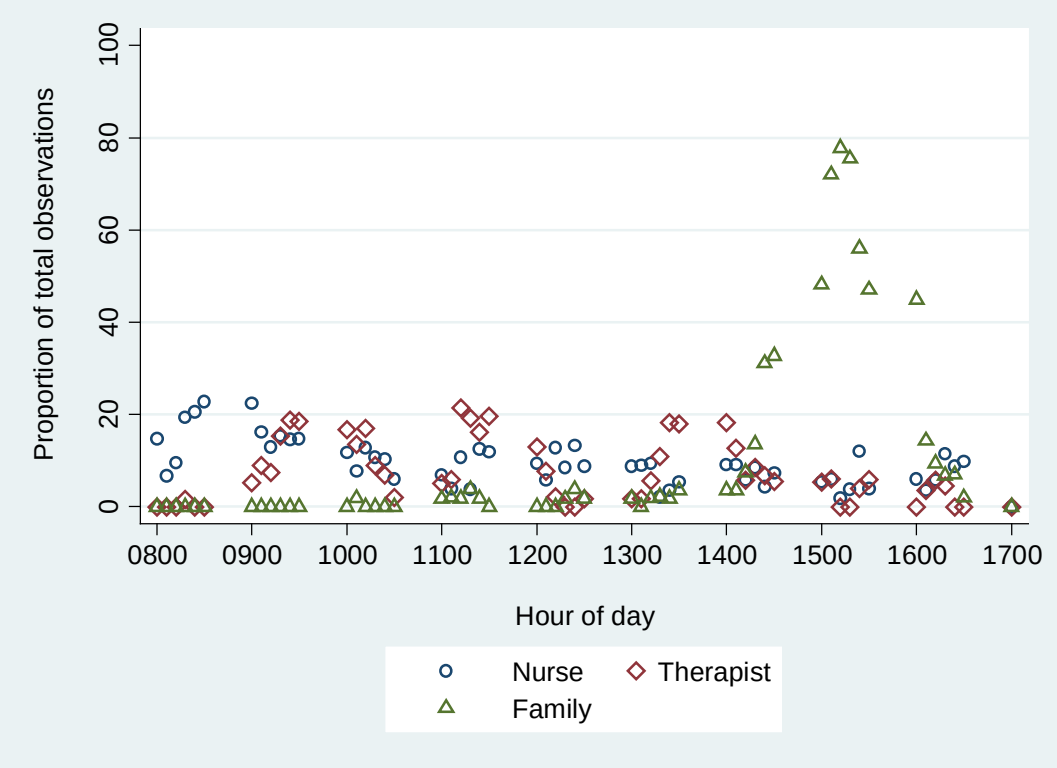
3.4.5 Person present with patient

Only the BMT data were used in this section. The patients were observed alone for the majority of time (60.1%). The professional group most frequently observed with the patient was nurses (9.5%) followed by physiotherapists (4.1%), occupational therapists (3.0%) and doctors (1.3%). Family were present 9.5% of the time. Patients were with doctors for a maximum of three consecutive observations, nurses a maximum of four observations, physiotherapists a maximum of six and occupational therapists a maximum of five consecutive observations. Table 3-8 shows data from observations with two or fewer people present. Most uni-disciplinary (two staff members from same professional discipline) interaction occurred between nurses and most multi-disciplinary interaction (two staff members from different professional disciplines) occurred between physiotherapists and occupational therapists. Nurses were observed most frequently with family members.

For each hour the proportion of therapists and nursing staff present does not exceed 25%. The number of therapists did tend to vary across the day, more so than for nurses. The presence of therapists was highest at 11:20 (21.4% of 56

observations) and, in the afternoon, at 14:00 and 14:10 (18.2% of 55 observations). The presence of nursing staff was highest at 08:50 (19.3% of 57 observations) and, in the afternoon at 12:40 (13.2%). The presence of therapists increases while that of the nurse decreases (Figure 3-8). Family were present between 14:30 and 16:00 which reflected visiting time.

Figure 3-8 Scatter plot of person present by hour of day (BMT data)



Blue circles represent the proportion of total observations that a nurse was present in each 10 minute epoch. Red squares represent the proportion of observations that a therapist was present in each 10 minute epoch. Green triangles represent the proportion of observations that family was present in each 10 minute epoch.

Table 3-8 Person type present with the patient (BMT data)

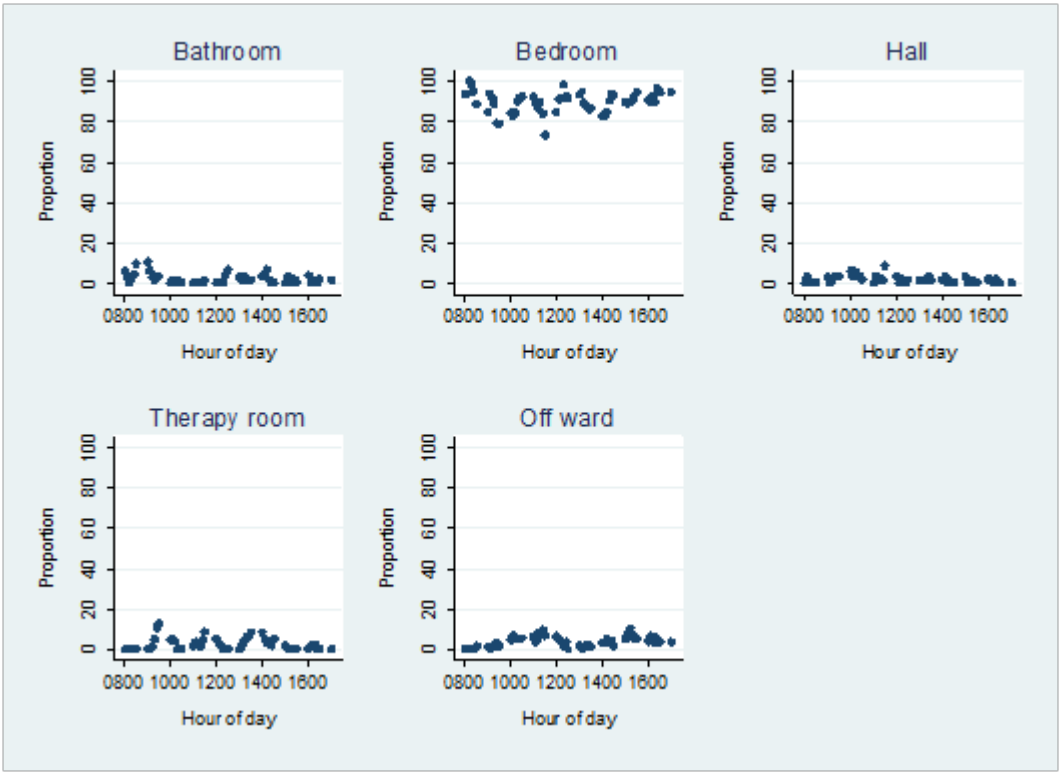
Person 1 type	Person 2 type Doctor	Nurse	PT	OT	ST	Family	Porter	Other	Alone	Total (%)
Doctor	6	5	0	0	0	0	0	0	28	45(1.3)
Nurse		44	8	1	0	13	0	1	213	329(9.5)
Physiotherapist (PT)			18	16	2	1	0	2	77	142(4.1)
Occupational therapist (OT)				2	0	2	0	2	81	106(3.0)
Speech & language therapist (ST)					1	5	0	0	31	40(1.1)
Family							0	2	282	305(8.8)
Porter								1	14	15(0.4)
Other									118	126(3.6)
Patient alone										2092(60.1)

To be read across.
Row numbers refer to the number of times the person 1-person 2 combination occurred not the total number of staff present.
Column 'total' is the sum of the row (multiply by 2 where person1=person2) added to the column numbers i.e. total for nurses = (44 x 2) + 8 + 1 + 13 + 1 + 213 + 5

3.4.6 Patient location

Only the BMT data were used in this section. Patients were observed in the bedroom nearly 90% of the time. The proportion of total observations spent in the bedroom, therapy room, bathroom and hall were 89.9%, 2.5%, 2.1% and1.7% respectively. The time spent by patients off ward for medical tests was 3.7%. Patients were in the therapy room for between one (approximately 10 minutes) to five consecutive observations (approximately 50 minutes) and off the ward for between two (approximately 20 minutes) to 15 consecutive observations at any one time (approximately2.5 hours). Patients were most frequently observed in the bathroom between 08:00 and 09:50, reflected by the drop in patients observed in the bedroom at this time (Figure 3-9). Time spent in the hall showed little variation throughout the day. Most patients were observed in the therapy room at three points in the day; 09:50, 11:30 and 13:40. Most patients were off the ward at 11:40 and 15:20.

Figure 3-9 Scatter plots of patient location by time of day (BMT data)



The blue circles represent the proportion of observations the patient spent in that location measured by the BMT for each 10 minute epoch.

3.4.7 Upright activity, person present and location

The BMT data and the AC data were used in this section. The proportion of observations in which a nurse was present was more consistent than that of therapists throughout the day. Nurses are usually stationary on the ward while therapists tend to visit the ward to provide therapy and have periods when they are off the ward such as at lunch time and towards the end of the day (Figure 3-10 to Figure 3-12). Therapist presence is negligible before 08:50 and after 16:00. There are two peaks that reflect the provision of therapy, one in the morning and one in the afternoon correspond to a morning and afternoon treatment session. The highest proportion of nurses corresponded with a higher proportion of time spent upright, particularly between 08:00 to 09:30 during showering. The presence of therapists appears to be positively correlated with upright activity. At 09:40 the presence of therapists rises to 18.2% with patients spending 17.2% time upright and at 14:00 with therapists present 18.8% of the time and patients spending 13.6% time upright. Family tended to be present during visiting hours only and the reduction in time spent upright during 15:00 to 16:00 indicates that family do not seem to influence the upright activity of the patient.

Figure 3-10 Upright activity and nurses present (AC and BMT data)

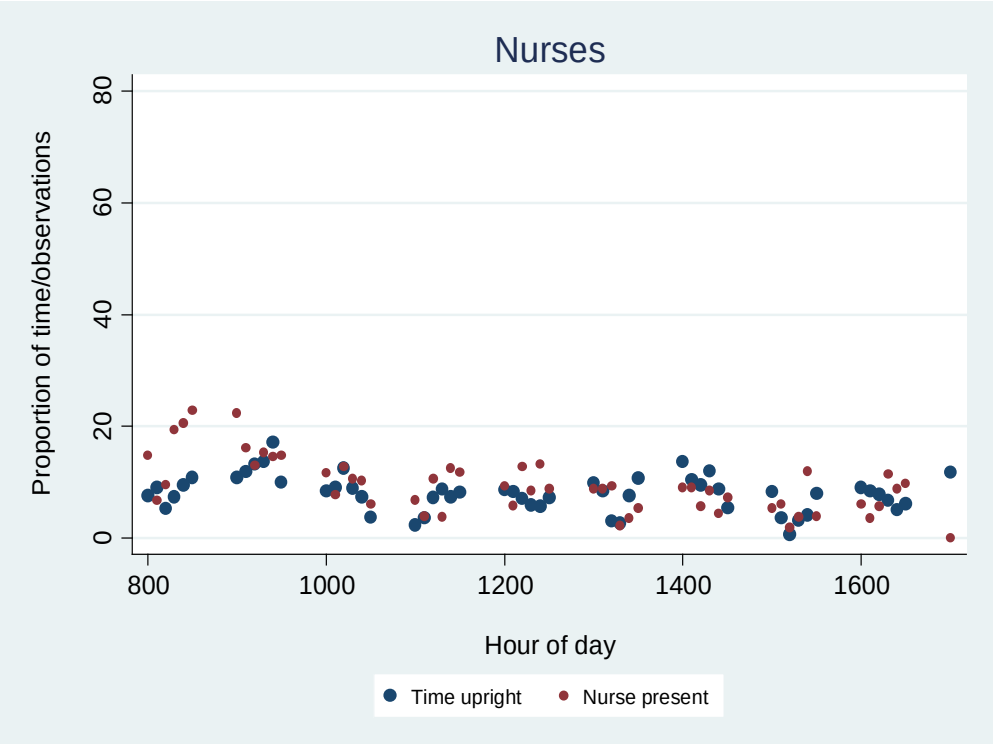


Figure 3-11 Upright activity and therapists present (AC and BMT data)

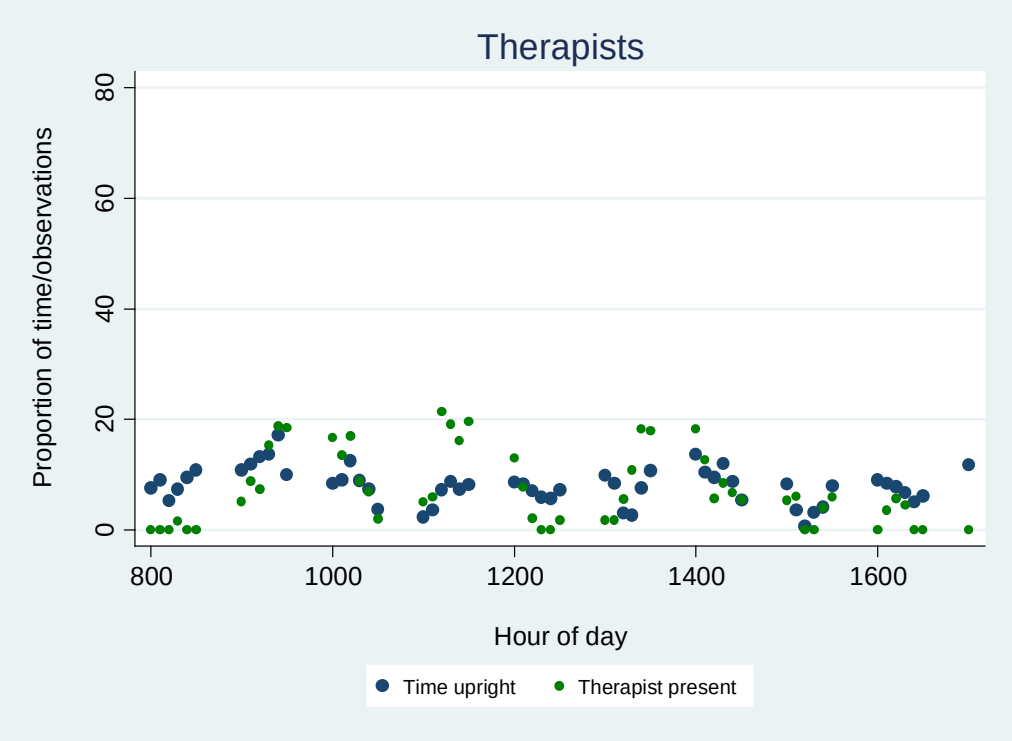


Figure 3-12 Upright activity and therapists present (AC and BMT data)

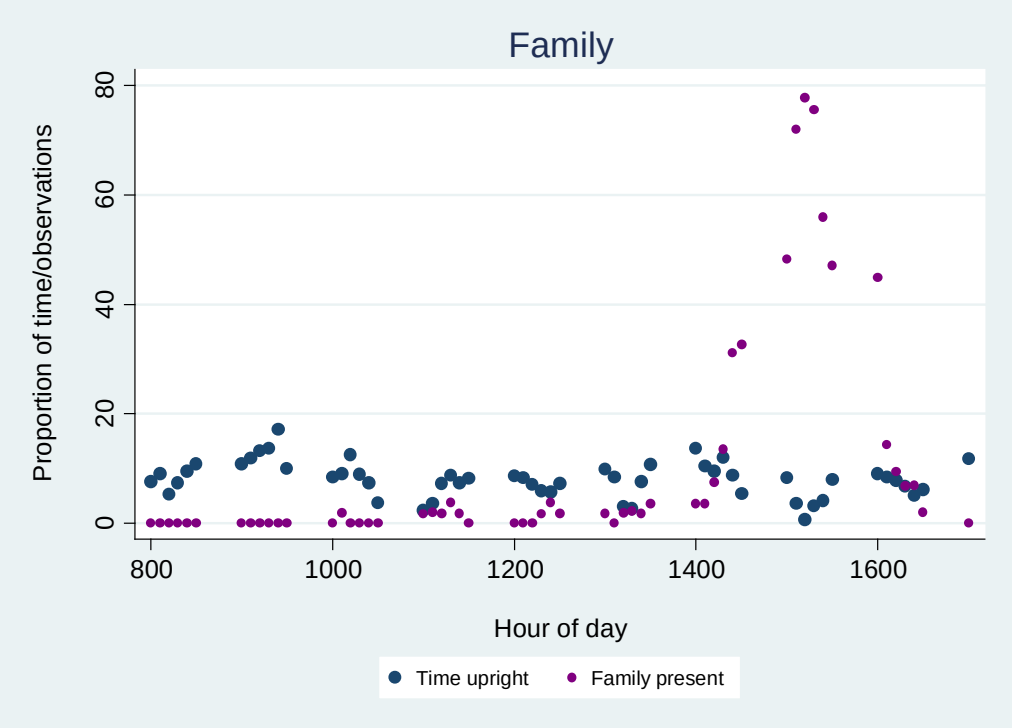
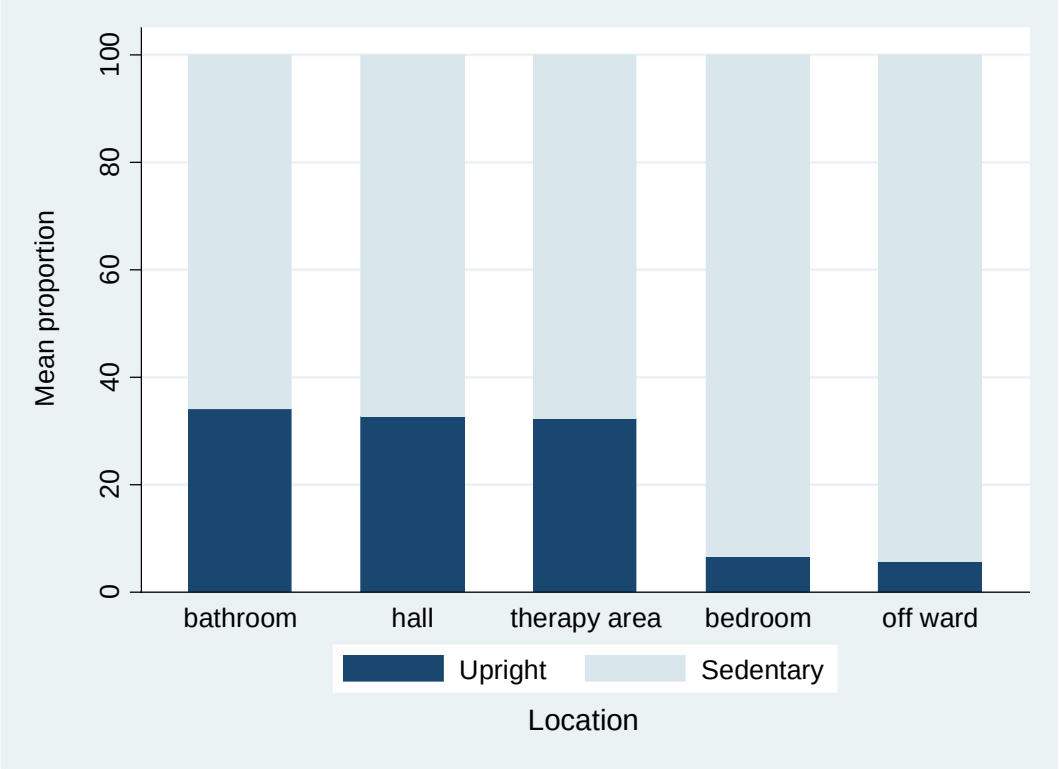


Figure 3 -10 to Figure 3 -12: Blue circles represent mean proportion of time spent upright measured by AC for each 10 minute epoch. Red circles represent the proportion of observations that a nurse was present for each 10 minute epoch as measured by the BMT. Green circles represent the proportion of observations that a therapist was present for each 10 minute epoch as measured by the BMT. Purple circles represent the proportion of observations that family was present for each 10 minute epoch as measured by the BMT.

As AC data does not provide information on the location of the patient during upright activity therefore the data from the two approaches were merged to quantify the amount of upright activity by location. The bathroom was the location with where most time was spent upright (34.1%) with similar levels of upright activity in the hall (32.7%) and the therapy area (32.3%). The least time spent upright was spent in the bedroom (6.5%) and during the time patients were observed to be off ward, predominately for tests (5.7%) (Figure 3-13).

Figure 3-13 Time spent upright by location (AC and BMT data)

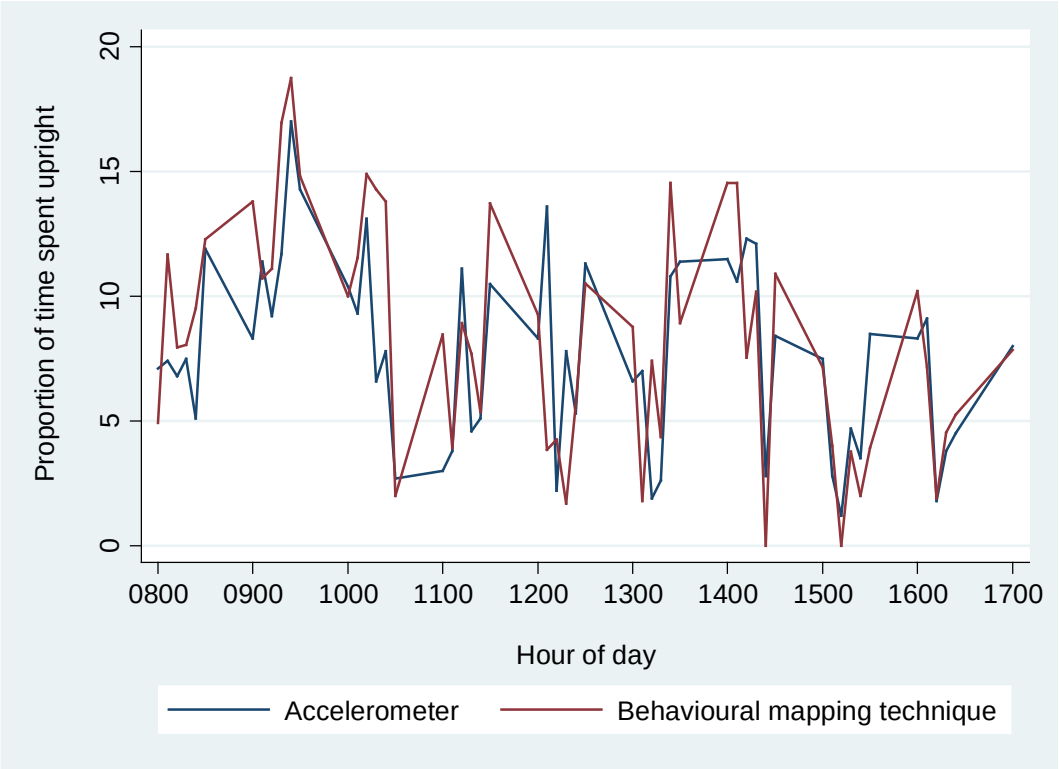


3.4.8 Predicting upright activity using accelerometry

Linear regression showed that the method of AC was able to significantly predict upright activity as measured by the BMT (coefficient 0.86, 95% CI, 0.62 to 1.10); $p < 0.01$ $R^2 = 0.6$). On visual inspection, accelerometry and the BMT showed similar measurements of upright activity throughout the monitoring period (Figure 3-14). However, there were times that the BMT measured a higher level of upright activity than the AC particularly at 08:40, between 10:30 and 11:10 and between 13:00 and 14:00. These times were often points when the patient

was not observable such as in the bathroom or during therapy. This time spent upright may be a result of the BMT recordings being based on recall.

Figure 3-14 Agreement of upright activity between AC and BMT



Upright as measured by the AC is the time spent upright in seconds as a proportion of the total monitoring time for each 60 second time interval i.e. 08:00:00-08:01:00, 08:10:00-08:11:00. Upright as measured by the BMT is the number of times upright as a proportion of the total number of observations at each BMT observation i.e. 08:00-08:01, 08:10-08:11.

3.4.9 Predictors of upright activity

Linear regression was used to identify which of the pre-specified patient and stroke characteristics were predictive of time spent upright. The variables predictive of activity included the NIHSS stroke severity score and the MSAS walking score. A reduction in activity is significantly associated with an increase in NIHSS score (higher severity).An increase in activity is significantly associated with an increase in MSAS score (higher function). A one point increase in NIHSS score resulted in 0.2% reduction in upright physical activity while an increase of one point of the MSAS score resulted in 0.1% increase in activity (Table 3-9).

Table 3-9 Predictive factors of time spent upright

	Multivariate analysis		
	Coefficient	**p-value**	**95% CI**
Age (years)	0.00	0.94	0.03, 0.04
Stroke severity (NIHSS score)	-0.15	0.00	-0.22, -0.09
Mobility (MSAS score)	0.06	0.02	0.01, 0.12
Time from stroke (days)	-0.09	0.10	-0.19, 0.02
Family present	-0.00	1.00	-0.05, 0.04
Previous stroke	0.02	0.86	-1.06, 1.11

3.4.10 Upright activity as a predictor of functional outcome

The number of patients independent in ADL at three months was 27 (42.9%) and at six months was 30 (47.6%). Logistic regression was used to assess the independent effect of upright activity on independent function at three and six months. Baseline level of disability (mRS) was the only factor significantly associated with independence at both three and six months and was, therefore, included in the two final multivariate models (Tables 3-10 and 3-11). Stroke type was significantly associated with independence at six months on univariate analysis so was also included in the model for function at 6 months. Upright activity did not have an independent association with independence at three months (OR 1.02, 95% CI 0.94 to 1.09) or six months (OR 1.02, 95% CI 0.95 to 1.10).

Table 3-10 Logistic regression models for function at 3 months

	Univariate analysis			Multivariate analysis		
	Coefficient	**p-value**	**95% CI**	**Coefficient**	**p-value**	**95% CI**
% upright activity	0.04	0.21	-0.02, 0.11	0.02	0.66	-0.10, 0.09
Age	-0.03	0.22	-0.08, 0.02			
Stroke type (TACS)	-0.36	0.84	-1.52, 1.24			
Living alone	-0.36	0.50	-1.40, 0.68			
Disability (high)*	-1.45	0.02	-2.67, 0.23	-1.38	0.04	-2.68, -0.08
Function (low)	-0.90	0.14	-2.10, 0.29			
Severity (moderate/severe)	0.13	0.82	-0.94, 1.20			

* Entered into multivariate model
TACS: Total Anterior Circulation Syndrome
Disability (high) is defined as mRS score >3
Function (low) is defined as BI score <18
Severity (moderate/severe) as defined by NIHSS score ≥8

Table 3-11 Logistic regression models for function at 6 months

	Univariate analysis			Multivariate analysis		
	Coefficient	**p-value**	**95% CI**	**Coefficient**	**p-value**	**95% CI**
% upright activity	0.05	0.19	-0.02, 0.11	0.02	0.55	-0.05, 0.10
Age	-0.03	0.28	-0.08, 0.02			
Stroke type (TACS)	-0.40	0.60	-1.74, 1.01			
Living alone	-0.51	0.33	-1.53, 0.51			
Disability (high)*	-1.32	0.03	-2.52, -0.12	-1.21	0.06	-2.50, 0.06
Function (low)	-0.88	0.14	-2.10, 0.30			
Severity (moderate/severe)	-0.01	0.98	-1.09, 1.06			

* Entered into multivariate model
TACS: Total Anterior Circulation Syndrome
Disability (high) is defined as mRS score >3
Function (low) is defined as BI score <18
Severity (moderate/severe) is defined as NIHSS score ≥8

3.5 Discussion

Key findings: levels of physical activity

A precise estimate of the time spent upright (standing or walking) was found to be 8.2% over a nine hour day. This was based on a sample of acute stroke patients from three Scottish hospitals. A study conducted by Lincoln et al (1996) 16 years ago using a BMT estimated time spent standing as 2.3% over an eight hour day, nearly a third lower than that estimated in this research.[105] Changes in practice over time and differences in study populations may explain this difference; the inclusion criteria used by Lincoln et al (1996) was more stringent excluding patients based on previous disability and those that required assistance of more than two nurses. A recent systematic review which pooled the findings from 15 studies that used a BMT reported that the median proportion of time spent inactive by patients was 48.1%.[128] The median proportion of time spent in moderate to high physical activity was 21.0%. The data from this study were recategorised according to activity classifications used in the review. This comparison revealed that patients in this study spent less time inactive (26.0%) and less time in moderate to high (12.9%) physical activity than the patients included in the review. Patients spent more time in low activity in this study, that is sitting in a chair, than the pooled estimate (53.2% versus 27.5%). There was a large amount of variation between the studies included in the review in terms of study population, the research setting, classification of activities and management of non-observed periods. Intra-patient variation (hour-to-hour differences within patients) was apparent across the day and most likely associated with the routine proceedings of the ward. Inter-patient variation (true differences between patients) is likely to explain the wide IQRs, especially at times when upright activity increased, presented for each hour of monitoring. There were significant differences in the level of upright activity between the sites after adjusting for baseline level of severity and level of mobility (see Chapter 5 for further discussion).

The time spent sedentary (sitting or lying) was estimated as 91.8%. Patients spent the majority of sitting in a chair at the bedside with time spent sedentary accumulated through prolonged periods of time sitting greater than 60 minutes

at a time. Nearly all sedentary time for patients with moderate/severe stroke was accumulated in this way. A previous study of inpatients from a rehabilitation ward (n = 30) showed a similar pattern with regards to how time spent in sedentary behaviour was accumulated; the highest proportion of time spent sedentary was accumulated in epochs of greater than 60 minutes.[130] This study was different: the population was not exclusively stroke, patients were not monitored in the acute stage and those that required substantial assistance with mobility were excluded. Staff working in the ASUs adhered to a local protocol of 'up-to-sit', aiming to get patients mobilised, not only early after stroke, but as these results show, up sitting in a chair early on in the day, however, without much activity thereafter. The National Institute of Health and Clinical Excellence (NICE) Quality Stroke Standard Statement recommends that a minimum of 45 minutes of physiotherapy, occupational therapy and speech and language therapy is provided daily as required and as tolerated. The amount of time spent in therapy was not measured directly in this study. Time in the therapy room is not an accurate reflection of actual therapy time as therapy was often carried out at the bed side or in the hallway. Therefore, the presence of therapy staff could be used as a proxy to time spent in therapy. Other studies have shown that time spent in therapy in a rehabilitation centre is about one hour in the UK, which is almost half of that of other countries that have been studied.[108] It has been reported that therapists overestimate the time patients spend in therapy;[131] therefore time spent other than that in scheduled activities such as sitting time may be even harder to recall and may result in staff inaccurately measuring the time actually spent in one episode of sitting.

Key findings: levels of interaction between patients and staff

Multidisciplinary interaction between professional groups occurred most frequently between occupational therapists and physiotherapists and is likely to represent the occurrence of joint assessments or co-mobilisation of patients with complex mobility requirements. Nurses were the professional group most frequently observed with the patient either working with each other and the patient (usually two nursing assistants) or working individually with the patient in the presence of another nurse i.e. trained nurses prescribing medications at the bedside with a nursing assistant present performing a different task with the

patient. The BMT does not provide data on the interactions between staff that occurred outside that observed in the presence of the patient. The amount of times staff were observed with family was surprisingly low considering the value that staff working in ASUs place on patient/family education and involvement and recognition as one of the most important changes that has occurred in stroke care (based on the qualitative findings presented in Chapter 5). Increased levels of upright activity were associated with the presence of nurses or therapy staff and reduced levels of upright activity were associated with the patient being alone or with family.

Key findings: the methods used to monitor activity

Accelerometry was able to significantly predict upright activity as measured by the BMT. Synchronising the AC and the BMT data sets in relation to time spent upright at each observed time-point throughout the day showed a good level of agreement between the two methods. It has been speculated that the algorithms used in the *activ*PAL™ may not detect stepping in patients without a defined heel strike or altered biomechanics, a feature common in an acute stroke patient's gait. Upright activity was the primary outcome in this study so the detection of stepping was of less importance. The possibly of this unfounded shortcoming of the *activ*PAL™ in explaining the low amount of time spent stepping presented in this study could not be ignored. An ad-hoc study to explore the sensitivity of the AC in detecting stepping was undertaken. It was noted that the type of researcher observation conducted in this study was not continuous; therefore no firm conclusions about the interchangeability of these two approaches in measuring activity could be drawn or assessed using a formal statistical analysis such as a Bland-Altman plots of agreement.[132]

Firstly, the exploratory analysis revealed that accelerometry had good concurrent validity with MSAS scores ($r = 0.6$, $p < 0.01$) and BI scores ($r = 0.8$, $p < 0.01$). The MSAS and BI are measurements of the patient's mobility/function and capability as opposed to activity and reality. Therefore, in order to make more of a direct comparison between the two methods, the degree to which each BMT observation activity (used here as the criterion measure) was detected correctly by AC was investigated using data from patients with uninterrupted recordings

for the full monitoring period (n = 41). The BMT data was time-matched with AC data for each one minute observation and indicator variables were created to indicate the occurrence of sitting, standing and stepping for each of the two sets of data. This analysis showed high agreement between BMT and AC with 98.6% (i.e. sensitivity = 1673/1696) of observations being correctly classified as sitting/lying by the AC. Agreement was slightly lower for standing with 75.0% (i.e. sensitivity = 48/64) of observations being correctly classified by the AC. Agreement between the BMT and AC for stepping was low with the AC classifying only 35.7% (15/42) of observations. Times of disagreement were further explored and, in the case of stepping, could be explained by the differences in methodology and that this was not designed to be a validity study. Reasons for the ACs apparent lack of sensitivity in detecting 27 stepping events was the result of stepping recorded when it occurred within 15 seconds of the one minute observation and was immediately followed by a transition (i.e. step to stand). Also, the stop-watch used for the BMT was not regularly calibrated with the computer used to programme the AC.

The need to investigate stepping, especially those with a slow gait needs to be further investigated. A study conducted in 2011 in Norway investigated the concurrent validity of *activ*PAL™ against video observations as the criterion measure. This study showed the *activ*PAL™ to be highly accurate in classifying lying, sitting and standing, however underestimated the step count during walking at slow speeds.[133] Therefore, a larger validation study using direct researcher observation or video analysis to test the accuracy of the *activ*PAL™ algorithms for use in the acute stroke population during gait-based activities and specifically for those patients with altered gait patterns is required.

Key findings: factors associated with activity and functional outcome

Generally, factors associated with decreased physical activity levels in older people have included increasing age, gender, obesity, disability, reduced education and social isolation.[134] This study identified that a high level of stroke severity and reduced mobility function were significantly associated with reduced levels of upright activity. These findings, although in agreement with a previous study,[46] should be considered cautiously as this study was not powered

to detect associations. A higher level of stroke severity at baseline and low level of walking have been associated with low levels of activity.[46] It has been speculated that activity levels have the potential to be influenced by the physical layout of units such as the amount of space available to move in. Patient interaction in this study occurred between patients of similar ages and may well be facilitated or inhibited by the layout of the ward. It was difficult to conclude whether rooms with four beds or an open plan ward encouraged interaction between patients as this depended on further factors such as stroke impairments especially speech and age. A previous study has suggested the use of tables in the bedrooms to encourage interaction, which may also increase activity.[108] This study has identified further patient factors that may have a role to play in the level of activity such as smoking status and certain personality traits. In this study it appeared that the patients that spent the most time upright were current smokers and frequented outside the hospital for a cigarette or patients that were considered 'fidgety' or to have a nervous/anxious disposition.

This study has shown that time spent upright does not appear to be predictive of independent function at three months and at six months. The level of upright activity undertaken in the acute stages between those that were independent and those that were not independent at three months was not significantly different. A recent study has shown activity in the acute stages post-stroke to have a favourable effect on outcome in stroke.[135] The sample was almost double the size of this study, consisted of more severely impaired patients, used BMT to measure activity and used the mRS scale as the outcome measure. These differences may account for these conflicting findings.

Strengths and limitations

The general inclusion criteria and the recruitment of patients from three ASUs provides the findings of this study with external validity. However, the number of patients recruited to the study with severe stroke impairment was low. The recruitment strategy aimed to be unselective, however recruitment of patients was not consecutive. The practicalities associated with one individual researcher recruiting patients across three sites may have resulted in patients, specifically

those that were considered on admission to be too unwell, being missed. For example, a patient who was reported as too unwell (and potentially more severely affected) and/or unsuitable to approach their relative so soon after diagnosis, required this patient or nearest relative to be followed-up at a later date. Yet, follow-up may not have been possible as recruitment may have occurred at another site or the patient may have been transferred onwards to a rehabilitation ward. Also, to ensure that patients were not burdened with invitations to participate in research studies it was agreed with the hospitals participating in the study that the patient after screening should only be approached for one research study. Although, it is unlikely that this specifically resulted in less patients with more severe stroke being recruited. Even with few eligibility criteria, recruitment can still be limited by the need to gain informed consent, especially for patients more severely affected.[136] Measures of stroke severity do not always portray the level of disability. In this study, over 45% of patients with mild stroke had a baseline mRS score of four or five.

Compliance with the study protocols was high. Patients frequently reported that they had "completely forgotten" that they were wearing the monitor, most likely due to its light-weight and non-invasive design. Technical failure did result in loss of data and is a limitation when using equipment to monitor physical activity. One patient, also the oldest, requested the *activ*PAL™ be removed towards the end of the monitoring period and detachment occurred in one of the three agitated patients. The feasibility and adherence to ACs requires further research in these patient groups. The BMT data were used to identify and clarify any anomalies in the AC data that were 'out-of-character'. As the BMT records data intermittently and incorporates breaks for the observer (the patient may have been unobserved for 20 minutes at a time) postural transitions may have been missed so cross-checking required assumptions and may have been the reason for the lack of congruence. The *activ*PAL™ itself is not waterproof which could be problematic when monitoring in a busy environment where staff have competing priorities. There is potential for monitors to be put on upside down (as in this study and reported in others) or not at all. Having a researcher present during the monitoring period undoubtedly minimised such occurrences. If the *activ*PAL™ monitor were to be used in routine acute stroke care such

practical issues alongside the financial implications need consideration. Advice to make the *activ*PAL™ waterproof is now available including the use of a medical grade adhesive covering such as tegaderm, yet these applications are in early use. As the *activ*PAL™ is uni-axial it does not distinguish between lying and sitting which may have important implications for this population. The *activ*PAL™ would not detect transitions where stroke patients were transferred using a hoist from lying in bed to sitting in a chair i.e. the patient was not upright during the transition. This was the case for one patient in this study and without the BMT data then for this patient then he would have appeared to have been lying in bed all day.

The BMT is designed to be as unobtrusive as possible, using distance observation and not intruding on patients behind closed doors or curtains. It is unlikely that patients altered their behaviour in response to being observed since the majority of patients who were able to walk required assistance to move, either with walking aids or the assistance of staff. Prior to commencing the study at each hospital it was explained to staff that the focus of the study was on how patients spend their time. It was also emphasised that there was no need for staff to change their way of working and that it was not their individual practice that was under evaluation.

There is a lack of a standard classification system for physical activity in stroke patients. In the healthy population physical activity is categorised by intensity (i.e. light, moderate, hard) determined by energy expended (as measured by metabolic equivalent [METs]). However, in the stroke population less is known about energy expended during activity. An alternative method to determining activity classifications using energy expended is to develop physical activity intensity-related AC cut-points specific to stroke patients. The number of minutes spent above a pre-specified threshold could then be translated as a measure of intensity, for example, low, moderate or high physical activity. As well as different definitions for the term 'physical activity' exist different definitions for the term 'sedentary' also exist. In research, the term sedentary has recently been defined by the Sedentary Behaviour Research Network as spending 'large amounts of time in behaviours that are of low energy expenditure (≤1.5 METs)' while in exercise science sedentary refers to the

absence of a moderate-to-vigorous-intensity physical activity.[137] However, applying this definition to the stroke population may not be reliable. The energy expenditure for a stroke patient whilst sitting may not satisfy the current definition of sedentary. Effort should be focused to explore the use of the term 'sedentary' in this population.

Implications for future monitoring and research

This study is distinct from other research investigating activity in acute stroke in that it measures activity using accelerometry, a method considered in its infancy in this population. It is further strengthened by the novel integration of another data source (the BMT) to provide objective data on other items such as the location of activity. New technical developments which combine accelerometry with global position systems allow the location of the physical activity to be tracked without the need for researcher observation. Researcher observation has been of value in provided insight into explaining certain patterns which is important in the planning, designing and implementation of new acute rehabilitation interventions. This research provides novel data on current activity levels for patients very early after stroke and for a Scottish healthcare setting. This is of relevance considering the current focus on the delivery of rehabilitation interventions rapidly to acute stroke patients.

The opportunity to measure physical activity in this population is not only important to identify associations between activity in these acute stages post-stroke and outcome but to monitor trends over time and evaluate the effectiveness or implementation of new rehabilitation interventions such as VEM. For example, a study conducted in 1980, investigated treatment patterns, solitary and social behaviour over two years.[103] The introduction of group exercise based therapy as opposed to that individually administered was illustrated by fewer peaks of treatment in year two. Information about the pattern of activity, therapeutic intensity of activities, person and location across the day provides a detailed picture of current practice. It offers a rich data source for a time-series evaluation to identify changes in practice or assess the longer term impact of new activity-based rehabilitation interventions. For example, the introduction of a longer working day may result in changes in

treatment patterns resulting in increased activity occurring later in the afternoon. With the development of new interventions or introduction of new practices it is important to embed rehabilitation-related process indicators into routine audits. This could provide opportunities for data linkage to assess, at a population level, the impact that the time of first mobilisation or the time spent in therapy in the acute stages has on (longer-term) outcome.

Future applications of accelerometry

Challenges exist with regards to selecting an appropriate monitor, how to manipulate, analyse and interpret AC data.[138] A recent review of studies that had investigated the clinimetric properties of accelerometry in patients in stroke identified 25 studies in which a range of AC devices, research settings and stroke populations were studied. It is difficult to determine from this the most appropriate AC and it may be that key discussions with manufacturers and the research team's budget influence choice. Presenting the median time spent upright for each hour to identify patterns of activity was considered sensitive to detect patterns over the day and to allow comparisons with other studies that have investigated activity over time.

Currently there are no reporting standards for studies using AC so this study has adhered to the limited guidance available and reported on items such as the number of wearing interruptions and detailed the decisions made regarding data analysis. It has been speculated elsewhere that the relationship between physical activity and sedentary behaviour is independent each having distinct correlates and patterns. The value of each of these outcomes and the relationships between them in the stroke population needs further investigation. For example, an increase in the time spent upright or the number of upright events does not necessarily mean a reduction in the number of sedentary bouts greater than 60 minutes. In this study, there was a non-significant association between total time spent upright and the number of sedentary events lasting between 30 to 60 minutes and greater than 60 minutes. It could be speculated that the relationship between upright activity and the accumulating of sedentary time is independent. For example, an increase in total time spent upright may not be related with an increase in the number of events in prolonged periods of

sedentary behaviour. This is important in developing interventions aimed at affecting activity patterns. Would an intervention aimed at increasing the amount of physical activity reduce the prolonged periods of sedentary time behaviour or are independent strategies required?

Accelerometry-based outcomes such as time spent upright could be used to measure the implementation (using process indicators) or effectiveness (using outcomes) of trial interventions aimed at increasing physical activity. A previous rehabilitation study aimed at doubling the amount of mobilisation practice to acute stroke patients resulted in a mean difference of 2.1% (95% CI -4.2 to 8.4) time spent upright measured by accelerometry between the control and intervention group. The mean difference does prompt discussion about defining and measuring clinically meaningful changes in upright activity which has implications for the monitoring of new rehabilitation interventions. Once determined, this expected mean difference could then be used to power future studies of interventions focused at increasing time spent upright. There is a need for further research to establish the clinimetric properties such as the predictive value and the responsiveness of AC-based measures in stroke before it can be considered gold standard in measuring activity in acute stroke patients or used as an outcome for change.[126] For example, improved knowledge of whether AC-based measures are able to predict outcomes such as disability is of value. These AC-based measures could then be recorded at baseline to assess a patient's suitability for inclusion into a study or for an intervention.

Future recommendations to increase activity levels in clinical practice

If activity-based interventions such as VEM are shown to be effective the focus will be to increase levels of upright activity and reduce prolonged sitting times at this important stage of neurological recovery. Recommendations to increase physical activity could include encouraging and assisting patients to engage in purposeful tasks to break up periods when patients are likely to be inactive, targeting times when the patient is known to be alone and sedentary i.e. at 11:00 and 13:30. Introducing a sense of 'normality' for patients such as the collection of their prescriptions from the nurse's station, going to the newspaper trolley to choose a newspaper or to greet relatives at the front door at visiting

time. Indeed it is noted that maximising opportunities for increasing upright activity and minimising sedentary periods for patients that are more severely affected may be more of a challenge as these patients often require external assistance of staff and equipment to mobilise. A flexible approach to implement such recommendations or strategies is required and consideration given to time of the day; for example, the nursing station was observed as a busy place in the morning but quieter in the afternoon possibly shaping the collection of prescriptions by patients as an afternoon service only. The use of volunteers or family members (the presence of family was strongly associated with sedentary behaviour in this study) and the revival of dayrooms. Some UK health board areas are currently recruiting volunteer ward visitors to provide stimulation and non-clinical support to patients who may not have family members close by.

There are perceived barriers to implementing strategies that involve family members and increasing activity levels such as HCPs' concerns over patient safety and perceptions of patient fatigue and capability as well as the patient's preference, motivation and ability. Education may be required to overcome these perceived barriers. The risks of prolonged sedentary behaviour should be included in patient and staff education sessions. Staff associated prolonged periods of time in one position with an adverse effect of muscle tone and believed that this should be interspersed with time in a lying position to stretch muscles.

Technological advances in mobile phones, wireless and interactive technologies in promoting physical activity are currently being used. Pedometer applications are now available for download to mobile phones. Connecting mobile phones to an AC to provide real-time feedback to the user are just some of the recent advances being used in public health initiatives.[139] The potential for the use of mobile phones is beginning to be recognised by HCPs to text reminder/feedback messages or also to monitoring and store activity data.

Certainly, in this study it was evident that patients didn't lose their connection with their mobile phones. They were often observed texting and talking on their mobile phone a number of times throughout the day. Mobile technology is primed to be the most powerful form of media to influence clinical practice in

the years to come. Using such wireless communication such as providing an opt-in text messaging service to stroke patient may be an option. Such text messages could be used to alert the patient of availability of hospital services such as the arrival of the newspaper trolley to the hospital ward or the availability of medications for collection from the nursing station. This is used here only as an example to highlight the potential technology may have in paving the way for a more stimulating ward pattern and breaking the mould of sedentary behaviour which has dominated stroke rehabilitation wards. Whether or not it would incentivise patients to engage in more physical activity and break up the bouts of sedentary behaviour, given that self-practicing of exercises was rarely observed in this study, is questionable. Additionally, and of course, there are questions, especially regarding sedentary behaviour, that would need to be addressed before such technological investment could be considered to target the current pattern of physical inactivity and sedentary behaviour and to supplement the education, support and communication already provided to acute stroke patients by HCPs.

3.6 Conclusion

This Chapter includes research that addresses the development stage of the Medical Research Council complex intervention framework. This observational data provides a baseline measure of activity levels in acute stroke patients. This will assist the evaluation of the future implementation of effective activity-based rehabilitation interventions such as very early mobilisation (VEM) in clinical practice. Appropriate methods of monitoring have been used and compared. Accelerometry-based measures such as time spent upright, time spent sedentary and how sedentary time is accumulated may prove to be valid process indicators to measure such implementation. The clinical problem of low levels of activity remains, however the prolonged periods of sedentary behaviour may be of more concern. Some strategies for use in clinical practice to increase activity levels have been suggested, however, it remains undetermined whether activity-based interventions such as VEM improve outcome. It is therefore important that the current evidence-base for VEM is investigated (Chapter 4).

4 Clinical impact of very early mobilisation

4.1 Introduction

Very early mobilisation is defined as mobilising patients up and out of bed (i.e. sitting out of bed, standing and walking) within 24 hours of stoke onset and continuing mobilisation at frequent intervals during the acute stage. Although early mobilisation of acute stroke patients is recommended in clinical guidelines,[2 42] VEM remains controversial and specific recommendations cannot be made until further evidence to guide practice is available. Due to its complex nature, standardising VEM poses a challenge in that the intervention actually delivered to the patient differs according to patient capability.

This issue of standardisation has important implications for approaches used in meta-analysis i.e. are the interventions comparable. Meta-analysis is defined as the "statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings."[140] Meta-analysis offers advantages for increasing statistical power and providing a more precise estimate of treatment effect than that of individual studies.[2] This approach has been used to determine the effectiveness of stroke rehabilitation interventions where the individual trials are often small in size and therefore underpowered. Generally, meta-analysis of aggregate data is often limited by poor or selective reporting. Additionally, as complex interventions are associated with issues of reproducibility, identifying and explaining clinical heterogeneity between studies using the 'same' intervention may pose further issues. Therefore, heterogeneity is considered a more pressing issue in the synthesis of complex interventions compared to that of drug interventions. Individual patient data meta-analysis may offer an alternative approach to identifying and explaining heterogeneity in complex intervention research. An IPD MA is defined as the collaborative collection of raw data from clinical trials that have addressed a common research question. To date, two phase II trials of VEM have already been conducted: the Australian AVERT phase II and the UK Very Early Rehabilitation or Intensive Telemetry after Stroke (VERITAS).[45 141] In order to maximise these existing data sources an IPD MA approach was employed to study the clinical impact of VEM which allowed for the adjustment

of key patient characteristics, to identify sources of heterogeneity between the studies and to explore the response to VEM in predefined subgroups of patients.

Chapter 3 highlighted that activity levels are low in acute stroke patients. Increasing activity levels in the acute stages post-stroke has been suggested to improve outcome. One activity-based rehabilitation intervention which aims to increase activity levels in the acute stages post-stroke is VEM. Very early mobilisation is under study in the ongoing AVERT phase III trial. As results from AVERT phase III are not available until 2013, this Chapter aims to explore the clinical impact of VEM using the best available evidence.

Aim

The aim of this IPD MA was to estimate the pooled effect of VEM in relation to pre-specified clinical outcomes. The primary outcome was independence at three months. In addition, the effect of VEM on stroke impairment, the risk of immobility-related complications and level of fatigue at one week post-stroke was investigated. Further secondary outcomes assessed at three months included the risk of immobility-related complications, death, discharge destination, ADL, mobility disability, health-related quality of life and resource use. The implementation of VEM was assessed using the following three process indicators; time to first mobilisation, total dose of mobilisation and mean time spent upright.

4.2 Methods

4.2.1 Trial selection

The latest Cochrane review (2009) entitled 'Very early versus delayed mobilisation after stroke' was used to identify trials of early mobilisation in stroke.[142] The aim of this previous systematic review was to establish the benefits and harm of VEM commenced within 48 hours of stroke onset in comparison with conventional mobilisation care. This review involved extensive searching of bibliographic databases, trial registers and hand searching of relevant journals. This review included "all randomised trials, with or without

blinding, of VEM within 48 hours of symptom onset compared with conventional care (that is, normal practice or no routine intervention." The participants in the studies were required to have "definite clinical diagnosis of stroke (focal neurological deficit of cerebrovascular origin) and could be mobilised within 48 hours of stroke onset. There were no age restrictions." The review identified three eligible trials, one completed; AVERT phase II and two that were currently underway at the time of the search; VERITAS and AVERT phase III. It should be noted that the VERITAS protocol had been intentionally matched to that of AVERT phase II in a number of key areas to ensure standardisation and in planning for this IPD MA.

4.2.2 Data collection and management

A prespecified analysis plan was provided to the researcher by the trialists in advance of collecting the individual patient data (IPD). This was used to establish the variables and outcome measures common to each dataset and to assess the data that could be combined (Table 4-1).

Table 4-1 Shared outcomes used in AVERT phase II and VERITAS

Shared outcome	Outcome measure	
Week 1		
	VERITAS	**AVERT phase II**
Stroke severity	National Institute Health Stroke Scale	Scandinavian Stroke Scale
Complications	Measured as per protocol	Measured as per protocol
Level of fatigue	Borg Perceived Exertion Scale	Borg Perceived Exertion Scale
Time to first mobilisation	Measured as per protocol	Measured as per protocol
Dose of mobilisation*	Time spent upright (accelerometry)	Time spent in therapy (therapist report)
Month 3		
Independence	Modified Rankin Scale	Modified Rankin Scale
Discharge date	Measured as per protocol	Measured as per protocol
Discharge destination	Measured as per protocol	Measured as per protocol
Complications	Measured as per protocol	Measured as per protocol
Activities of daily living	Barthel Index	Barthel Index
Level of mobility	Rivermead Mobility Index	Rivermead Mobility Index
Health-related quality of life	Assessment of Quality of Life Questionnaire	Assessment of Quality of Life Questionnaire
Resource use*	Measured as per protocol	Measured as per protocol

*Data were not aggregated

Annonymised data for the relevant baseline factors and prespecified outcomes were extracted from the AVERT phase II data set and the sub-set sent, as an Excel file, via email to the researcher. The VERITAS data were sent, in its entirety, as a statistical package file via email to the researcher. The data were cleaned, re-coded as required and cross-checked with reports and publications. The trial protocols were used to provide information about the intervention provided and the outcome measures (and versions) used in each of the trials. Data queries were raised and managed in collaboration with the relevant trialist.

Primary outcome and secondary outcomes at one week

The choice of outcomes was based on those used in the previous Cochrane review.[142] The primary outcome was independence at three months as measured by the Modified Rankin Score (mRS). The secondary outcomes measured at one week included stroke severity (National Institute Health Stroke Scale [NIHSS] or Scandinavian Stroke Scale [SSS]), complications of immobility in hospital and level of fatigue (Borg Exertion Scale [BORG]). The primary outcome was the proportion of patient's independent at three months as defined by a mRS score of ≤ 2. The original rankin scale consisted of five categories based on ability to perform certain activities as well as taking account of the level of assistance required. The modified version as it is widely used today is considered to be a measure of global disability and consists of two additional categories – 'no symptoms' and 'dead', providing a seven point scale.

The NIHSS is a 15 item neurological impairment scale with a maximum deficit score of 42 points.[143] The key aspects that are measured are eye movement, motor and sensory impairment and level of consciousness. The SSS is also a neurological impairment scale which incorporates an initial prognostic and long-term functional score. The key aspects that are measured include consciousness, eye movement, motor power, speech and facial palsy. The level of impairment for a patient is measured as a value between 0 and 58, with lower scores indicating greater impairment.[144] As stroke severity was measured using different outcome measures the SSS scores obtained for patients in AVERT phase II were converted to the NIHSS score using the following interconversion equation:[145] NIHSS score = 22.99 – (0.39 x SSS score). Complications were defined

as stroke related, immobility related, co-morbidity related or any others. Complications of immobility included falls, pneumonia, chest infection, deep venous thrombosis, pulmonary embolism and pressure sores. Complications were collected from medical records by a blinded assessor. The BORG is a self-rating scale used to measure perceived exertion during physical activity; it ranges from 6 to 20, where 6 equals "no exertion at all' and 20 equals "maximal exertion".[146] Excessive fatigue was defined as a score of >13 "somewhat hard".

Secondary outcomes at three months

The further prespecified secondary outcomes measured at three months included mobility (Rivermead Mobility Index [RMI]), place of discharge, death, activities of daily living (BI), health-related quality of life (Assessment Quality of Life [AQoL)) and resource use. The Rivermead Mobility Item comprises of 14 items with activities ranging from turning over to running.[147] Each question is answered either yes (score = 1) or no (score = 0) with a maximum score of 14. A lower score indicates a greater mobility disability. Non-impaired mobility was defined as a RMI score of 10 to 13. Discharge destination was categorised as home, rehabilitation unit/ward, acute hospitalisation, sheltered housing or a nursing home. Return home was defined as patients who were previously living in private residence and had returned to this living arrangement by month three. The BI measures performance of ADL. It is a 10 item scale which ranges from 0 to 100, where lower scores indicate greater dependency. This score is often re-scaled from 0 to 20, with each item divided by five. Independence was defined as a BI score ≥ 18. Patients who had died were assigned a score of zero.

The AQoL is a utility instrument which measures health-related quality of life (HRQoL)[148] comprising of 15-items and five domains as follows; illness, independent living, social relationships, physical senses and psychological wellbeing. Responses to each of the AQoL items were summed to provide value profiles of illness, independent living, social relationships, physical senses and psychological wellbeing. Patients who died were assigned a score of zero. This coding created scores for each scale ranging from '0–9', where '0' represents 'normal' or 'good' HRQoL and '9' the worst possible HRQoL for each dimension. These scores were then summed to provide an overall unweighted HRQoL-index,

where overall AQoL scores ranged from '0–45', where '0' represents 'normal' or 'good' HRQoL and '45' the worst possible AQoL HRQoL-score. The AQoL score is then used to compute an overall utility score weighted by preference in order to calculate quality-adjusted life years (QALYs) for use in economic evaluation. The conversion of the unweighted HRQoL scores to utilities for use in economic evaluation is presented in Chapter 6.

Resource use was determined by a blinded assessor during a face-to-face interview with the patient or nearest relative and by retrieving information about hospital re-admissions from medical records at three months post-stroke. The specific resource items varied between the trials; in both trials resource use information on initial acute hospital length of stay (LOS), hospital re-admission LOS and some aspects of care provided in the community were gathered. Generally, there is no consensus regarding the methods to pool multinational resource data or resource data from different hospitals for meta-analysis or economic evaluation. Resource use is highly variable between countries due to differences in healthcare systems. Combining resource data for a meta-analysis is controversial and may limit the generalisability of estimates of cost and by implication estimates of cost-effectiveness across settings.[149] Considering this and the variation in resource use that existed between the two studies for the purpose of this IPD MA of resource use was not considered appropriate. Therefore, the summary data available from the published sources were extracted, tabulated and described. A planned economic evaluation alongside AVERT phase II has already been conducted and has since been published.[150]

Process indicators are markers defined to assess the quality of care and benchmark the implementation of guidelines.[151] Two process indicators were used in this analysis; time to first mobilisation after stroke onset and the amount of mobilisation activity. In order to measure time spent in mobilisation activity in AVERT phase II trial staff recorded time with a therapist doing mobilisation (VEM) and time spent in SC (control). This was measured for the intervention period of 14 days or earlier if the patient was discharged. In AVERT phase II the total dose of mobilisation for each treatment group (in minutes) across the length of stay was calculated. In VERITAS an AC was used to measure time (in minutes) spent in sitting/lying, standing and stepping for patients. This was

measured on days three, four and five with recordings on the first day considered most reliable due to the lower levels of missing data on that day. In VERITAS time spent upright, defined as the time spent standing or stepping, was calculated. As the methods of measuring mobilisation activity were different in each of the trials the data for this process indicator were not combined.

4.2.3 Statistical analysis

Analyses included all patients and used an intention to treat approach. Baseline patient characteristics were described for each trial and summarised in the two treatment groups. Univariate analysis was used to compare patient characteristics at baseline and the time to first mobilisation between the two individual trials and between treatment groups in the IPD MA. Where data were not normally distributed (stroke severity scores, time to first mobilisation and length of stay), the Wilcoxon-Mann-Whitney test, a nonparametric equality of medians test was used.[152] Time spent mobilising was compared between the treatment groups using summary data from the trials. The conventional level of significance ($p \leq 0.05$) was used.

The methods for meta-analysis for aggregate data are well-developed with a number of approaches available depending on the assumptions being made regarding a common treatment effect between the included studies. For IPD MA two main types of analysis are recognised; the one-stage analysis and the two-stage analysis. The one-stage analysis combines all the IPD from the studies and models the treatment effect simultaneously. The alternative approach is the two-stage approach whereby a summary estimate is calculated for each individual trial and synthesised using traditional meta-analysis. For analysis in this Chapter the two-staged approach was used to assess the treatment effect. The outcomes were analysed for each of the trials and then these individual summaries were used to provide an overall measure of effect. A common treatment effect was assumed therefore it was appropriate to use a fixed effect model. Analyses were also run using a random effects model (DerSimonian and Laird, 1986[153]) to cross-examine the robustness of this assumption. The treatment effect was calculated using the Mantel-Haenszel method which combines on the log scale, ORs for each trial using a weighting scheme based on

the inverse of their variance. The random effects model, in assessing uncertainty incorporates an additional measure of between-study variation. For continuous factors (stroke severity and HRQoL scores) a weighted mean difference was calculated. For stroke severity, patients who died were excluded from the analysis. The amount of heterogeneity was assessed visually using forest plots and quantified using the I^2 statistic, which describes the percentage of variation between studies due to heterogeneity rather than chance.[154] An available guide for the approximate interpretation of the I^2 statistic was used; low = 25%, moderate = 50% and 75% = high.[154]

Multivariate logistic regression was used to assess the effect of VEM on independence at three months adjusting for patient and stroke characteristics known to effect outcome. The identity of each trial was upheld within the model so as to preserve clustering of patients within studies and allowed inferences to be based on the randomisation of patients within each trial.[155] In multivariate analysis adjustments were made for known confounders including age, baseline stroke severity and pre-morbid disability. Age, baseline severity and the level of disability on admission have been identified as factors affecting recovery.[156 157] The effect of including additional factors, as informed by the univariate analysis ($p < 0.10$) was also explored in separate models. As the number of patients was small the most parsimonious model was selected. A similar method of univariate and multivariate analysis was carried out for the secondary outcomes.

Similarly, the same approaches (either the one or two-stage) can be used to examine the effect of covariates. A two-staged approach was used in this analysis to conduct a subgroup analysis where patients within each trial were grouped into prespecified categories and the treatment effect was estimated across the trials for each of the subgroups. This subgroup analysis allowed the exploration of whether groups of patients with similar characteristics from two separate trials respond in the same manner to the intervention. Subgroup analysis was restricted to the primary outcome and based on prespecified groups that were identified in each trial as important patient characteristics for adjustment in the final analysis of outcome, these included age, stroke severity at baseline and pre-morbid disability. The patient groups were defined as (i) patients with a mild stroke (NIHSS ≤ 7) or moderate to severe stroke (NIHSS > 8),

(moderate and severe categories were collapsed due to the low number of events in the severe category), (ii) patients aged < 75years or ≥ 75years (iii) patients with no or mild previous symptoms (premorbid mRS, 0 - 1) or patients with moderate previous disability (premorbid mRS, 2 - 3). Subgroup interaction was tested between patient groups using the chi-squared statistic.[149]

4.2.4 Ethical approval

Each trial had separate protocols approved by National research ethics committees. Informed consent was gained from each patient or their next of kin. As the research questions of this IPD MA are addressing the same question as the original trials, ethical approval had already been sought. This IPD MA is potentially providing a more reliable answer to the question that the patient originally consented to when entering the trial, therefore the same consent applies. All data sent to the researcher by the trialist were de-identified.

4.3 Results

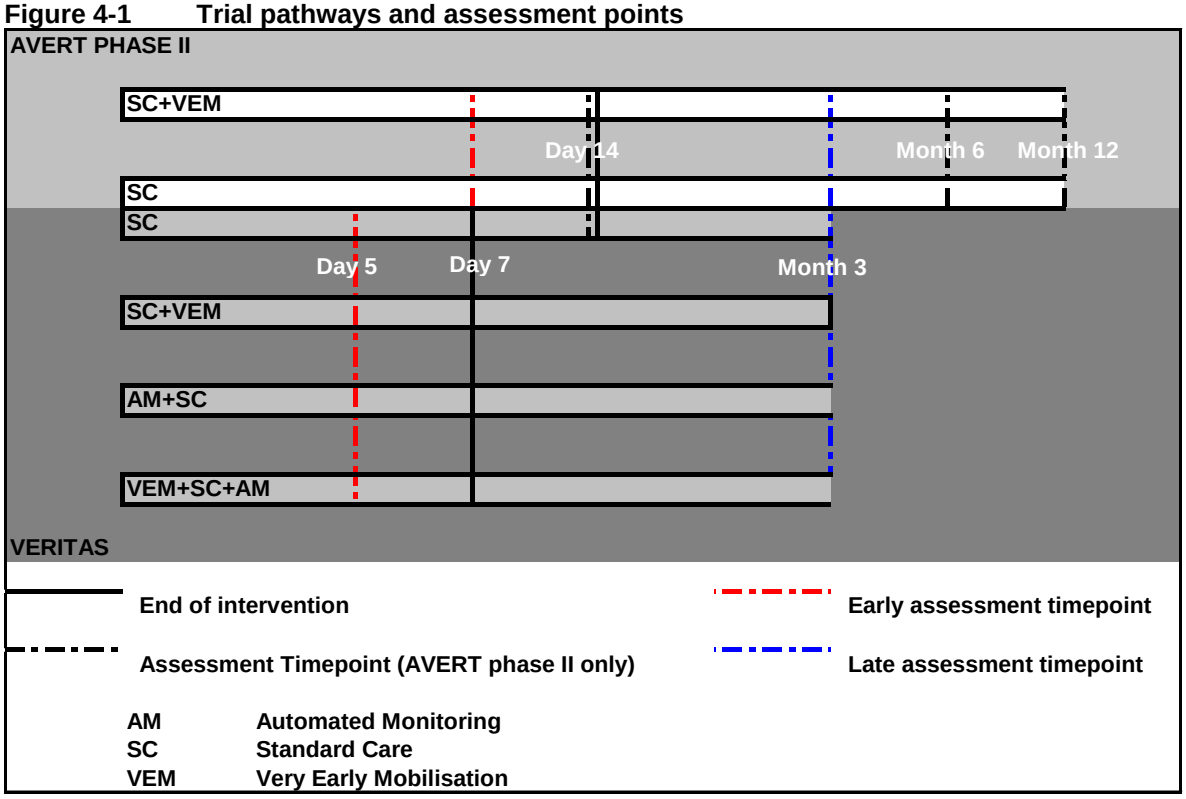
4.3.1 Trial characteristics

The completed trial (AVERT phase II) and the (since completed) VERITAS trial as identified by the Cochrane review were included in the IPD MA. At the time of pooling these data AVERT phase III was ongoing. This IPD MA commenced on completion of the VERITAS trial and after both trial reports had been accepted for publication. A Very Early Rehabilitation Trial phase II and VERITAS were both designed to compare the feasibility and safety of a VEM protocol with usual stroke care mobilisation practices. A Very Early Rehabilitation Trial phase II was a multicentre randomised trial conducted at two hospital sites in Australia between 2004 and 2006. The Very Early Rehabilitation or Intensive Telemetry after Stroke trial was a single centre randomised trial conducted in Scotland between 2006 and 2007 and used 2 x 2 factorial design to investigate the combined effect of VEM and automated physiological monitoring. The key principles of the VEM intervention protocol used in AVERT phase II were adopted in VERITAS with respect to the timing, nature and frequency of the intervention. Both trials aimed to get patients up to sit, stand and walk within 24 hours or as soon after the point of recruitment as possible and continued mobilisation

throughout the day. The time to trial recruitment from onset of stroke symptoms was slightly shorter in AVERT phase II (< 24 hours) to that of VERITAS (< 36 hours). Very Early Mobilisation was delivered for 14 days by a team of both nurses and therapists in AVERT phase II and was predominately nurse-led for seven days in VERITAS. Standard care at the hospital sites was similar in that patients were transferred to a stroke unit where staff with specialist skills in stroke and had regular MDT meetings. Routine physiological monitoring occurred ever four hours and mobilisation was provided by ward therapists and nurses.

Patients recruited to VERITAS were randomised to one of four groups; SC, early mobilisation, automated physiological monitoring (AM) or AM and early mobilisation. Automated physiological monitoring involved the use of a commercial monitoring system and a well-developed protocol to continuously monitor patients and provide advice on managing irregularities in heart rate, blood pressure, temperature, oxygen saturation or blood glucose. This mode of monitoring was conducted for the first three days post-stroke, thereafter patients reverted to SC. Both trials used computer generated, blocked randomisation procedures and used opaque envelopes to conceal group allocation. In AVERT phase II, patients were stratified by stroke severity and hospital site. The inclusion and exclusion criteria were similar for both trials. In both trials patients aged over 18 years with a new or recurrent stroke were recruited and patients with severe pre-stroke disability or co-morbidities (severe heart failure, other progressive neurological disorder, acute coronary syndrome or confirmed/suspected lower limb fracture) were excluded. In AVERT phase II severe pre-stroke disability was defined as a pre-morbid mRS score >3 and in VERITAS it was defined as a pre-morbid mRS score > 2. There was no upper age limit in either trial. Data were available for all recruited patients. Outcome assessment was conducted on day seven and 14 post-stroke then on month three, six and 12 months. In VERITAS outcome assessment was carried out on day five, at discharge and then at three months (Figure 4-1).

Figure 4-1 Trial pathways and assessment points



4.3.2 Patients characteristics

All patients in AVERT phase II (n = 71) and VERITAS (n = 32) were included in the IPD MA. No patients were lost to follow-up at three months. AVERT phase II had 33 patients in the SC group and 38 patients in the VEM group while VERITAS had eight patients in each of the four treatment group, 16 patients received early mobilisation and 16 patients received standard mobilisation practices. The pooled analysis showed the baseline characteristics of patients were comparable between treatment groups (Table 4-2). It is worth noting that VERITAS excluded patients with mRS > 2, therefore the number of patients in the mild to moderate disability category (premorbid mRS 2 - 3) was small. Furthermore, there were some differences in the patient baseline characteristics between the two trials. VERITAS patients had a lower mean age than AVERT phase II patients (65.3 years versus 74.7 years). AVERT phase II had a higher proportion of patients with risk factors for stroke than VERITAS – hypertension (70.4% versus 37.5%), atrial fibrillation (31.0% versus 6.2%) and current smokers (40.6% versus 14.1%). More patients had moderate or severe stroke in AVERT phase II than VERITAS (57.8% versus 28.1%). The proportion of patients in AVERT phase II with TACS was higher than that of VERITAS (22.5% versus 9.4%).

Table 4-2 Patient demographics and stroke characteristics by group

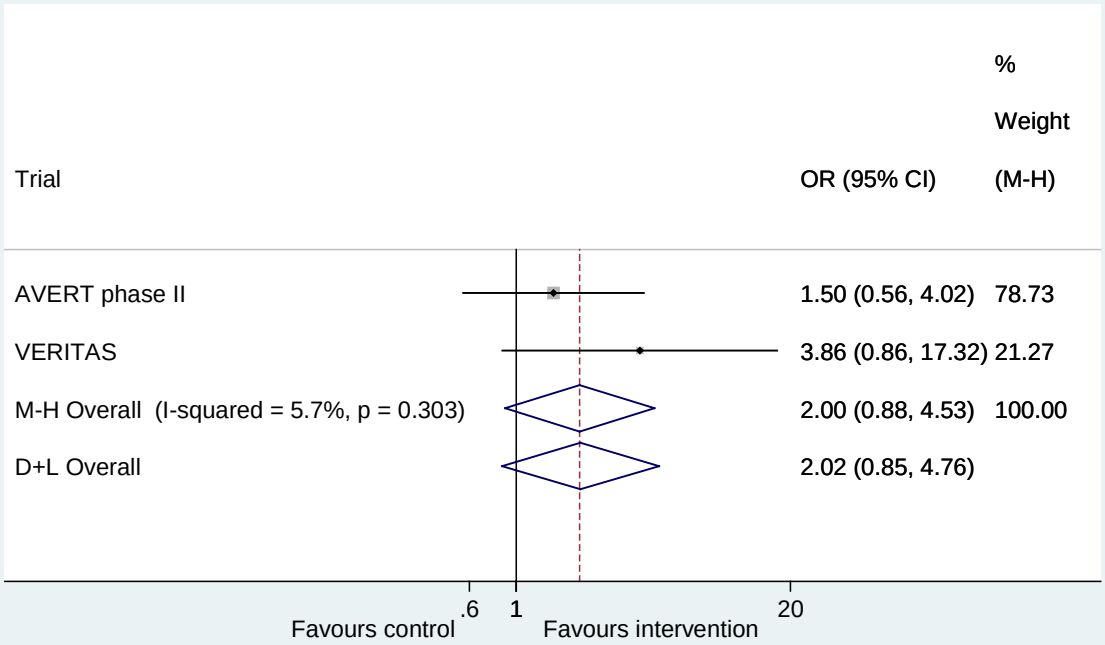
	SC	VEM	p-value
Number of patients	49	54	
Age (mean, SD)	72.0 (11.6)	71.6 (14.2)	0.86
Female	27(55.1%)	22(40.7%)	0.15
Stroke risk factors			
Hypertension	32(65.3%)	30(55.6%)	0.31
Atrial fibrillation	12(24.5%)	12(22.2%)	0.79
Coronary heart disease	18(36.7%)	11(20.4%)	0.07
Diabetes	7 (14.3%)	13(24.1%)	0.21
Current Smoker			
Yes	13(26.5%)	10(15.5%)	0.33
No	36(73.5%)	44(81.5%)	
Premorbidity (mRS score)			
No or mild symptoms (0-1)	41(83.7%)	39(72.2%)	0.16
Mild-moderate disability (2-3)	8(16.3%)	15(27.8%)	
Living arrangements on admission			
Home alone	17(34.7%)	11(20.4%)	0.24
Home not alone	30(61.2%)	39(72.2%)	
Other	2(4.8%)	4(7.4%)	
Stroke history			
Previous stroke	7(14.3)	15(27.8)	0.10
NIHSS score			
Total Score (median, IQR)	8(4-12)	6.5(3-13)	0.90
Mild (1–7)	24(49.0%)	29(53.7%)	
Moderate/Severe (>8)	25(51.0%)	25(46.3%)	
Oxfordshire classification			
TACS	9(18.4%)	10(18.5%)	0.21
PACS	17(34.7%)	17(31.5%)	
LACS	10(20.4%)	10(18.5%)	
POCS	5 (10.2%)	14(25.9%)	
ICH	6 (12.2%)	3 (5.6%)	
Unknown	2(4.1%)	0 (0%)	

Entries are n (%), unless stated otherwise.
mRS; Modified Rankin Score, NIHSS; National Institute Health Stroke Scale. TACS - Total Anterior Circulation Syndrome; PACS - Partial Anterior Circulation Syndrome; LACS - Lacunar Circulation Syndrome; POCS - Posterior Circulation Syndrome; ICH - Intracerebral Haemorrhage.

4.3.3 Independence at three months

The proportion of VEM patients who were independent at three months was higher than the SC group (61.4% versus 38.6%). Very early mobilisation was shown to have a favourable effect on independence at three months (unadjusted OR 2.02 (0.85 to 4.76; p = 0.10) (Figure 4-2). The estimates from the random effects model and the fixed effects model were similar indicating that the assumption that the individual trials were estimating the same treatment effect was robust. The level of statistical heterogeneity between the studies in estimating independence was negligible (I^2 = 5.7%). After adjusting for baseline factors the effect size increased, with patients who underwent VEM were three times more likely to be independent at three months than SC patients (adjusted OR 3.11, 95% CI, 1.03 to 9.33; p = 0.04)**.** Coronary heart disease was the only factor to be significant (p = 0.07) on univariate analysis. The model when further adjusted for this factor was unaltered (adjusted OR 3.10, 95% CI, 1.02 to 9.30; p = 0.05) therefore was not included in final multivariate model.

Figure 4-2 Forest plot for independence (mRS) at 3 months

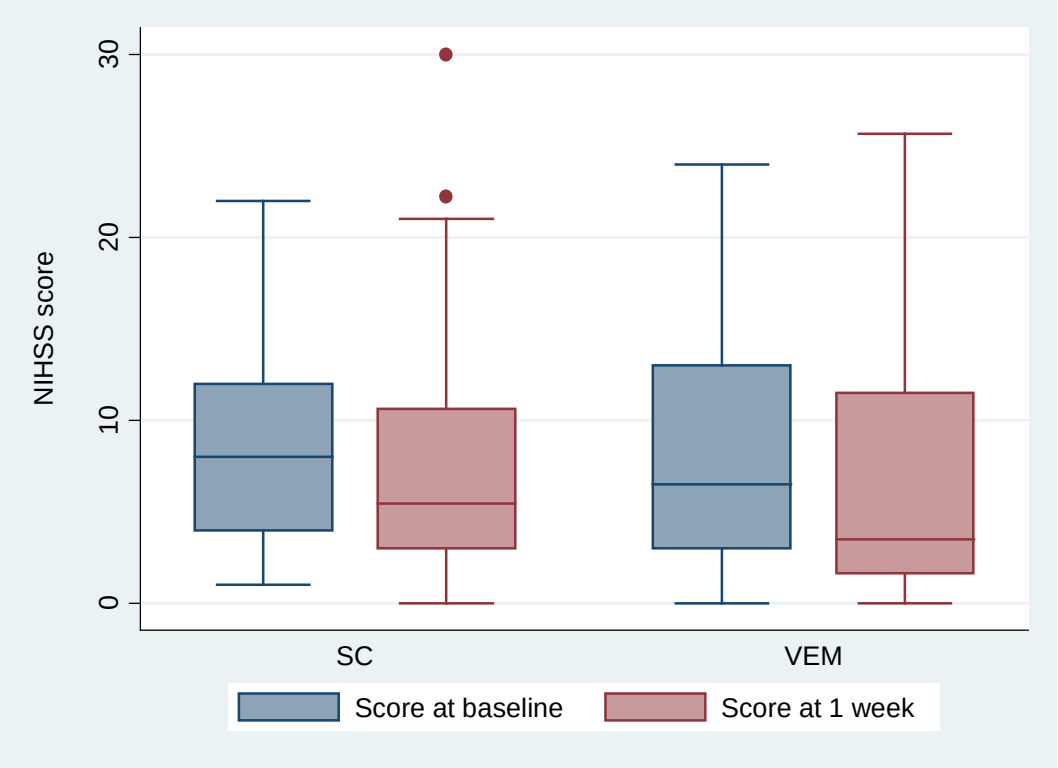


The effect size of each of the trials is shown by the black circle. The grey coloured box represents the weight given to the individual study. The size of the box is proportional to the weight given to each of the individual studies. The diamonds and the broken red line represent the overall summary estimate. The top diamond is the overall summary estimate using a fixed effects model (Mantel-Haenszel method, "M-H Overall"). The bottom diamond is the overall summary estimate using a random effects model (DerSimonian and Laird, "D+L Overall"). The black vertical line represents the null value of 1.

4.3.4 Secondary outcomes at one week

Both groups showed a reduction in NIHSS score from baseline to that measured at one week; this reduction was significant in the VEM group (p = 0.01). Patients undergoing SC had a median score of 8 (IQR 4 to 12) at baseline which reduced to median score of 5.5 (IQR 3 to 10.6) one week later. Patients who received VEM had a median score of 6.5 (IQR 3 to 13) at baseline which reduced to a median score of 3.5 (IQR 1.6 to 11.5) one week later (Figure 4-3). For both of the trials severity scores were lower in the VEM group than the SC group at one week, resulting in a negative difference in means The effect of treatment, after adjusting for covariates was non-significant (adjusted coefficient -0.59, 95% CI, -2.44 to 1.27; p = 0.53).

Figure 4-3 Boxplot of NIHSS scores by treatment group at 1 week



Number of patients = 97. The middle line in each of the boxes represents the median value. The bottom and top lines of each of the boxes represent the 25th and 75th percentiles. Values outside this are represented by the vertical bars. Extreme values (“outliers”) are represented by the circles.

A greater percentage of SC patients (51.0%) experienced at least one complication compared to VEM patients (35.2%) (Table 4-3).

Table 4-3 Immobility-related complications at 1 week

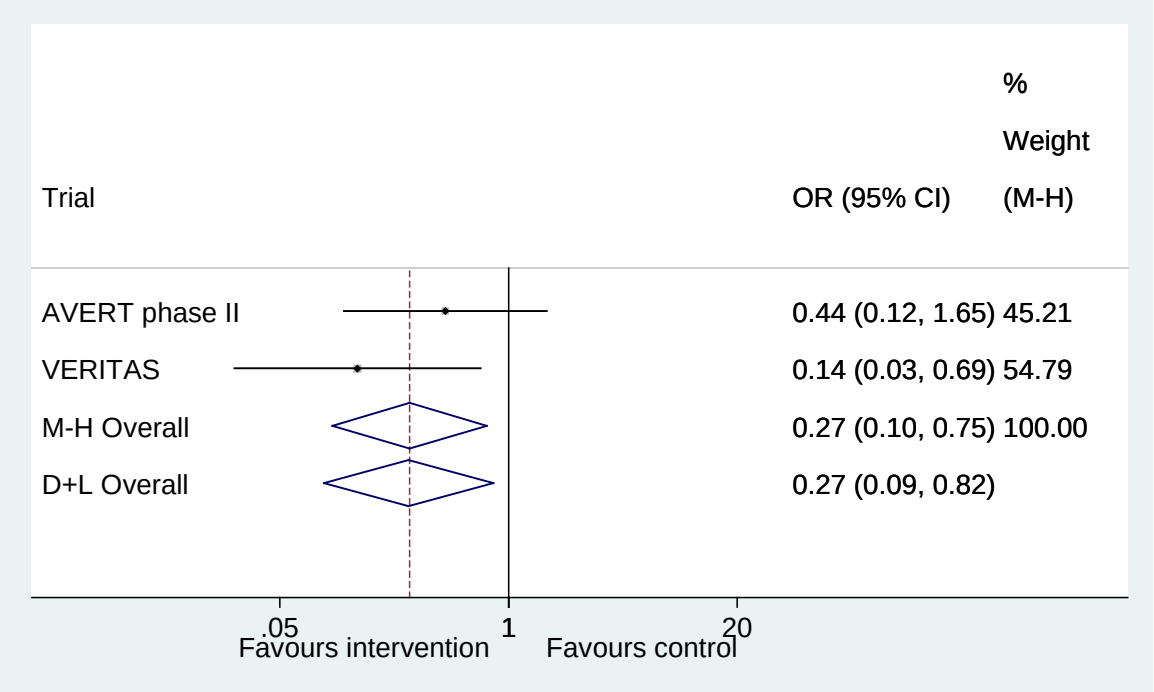
	SC (n=49)	VEM (n=54)	p-value
No of complications			
1	12	9	
2	5	6	
3	5	2	
4	2	1	
5	1	1	
Stroke-related complications			0.20
Death	1	4	
Progression	1	3	
Recurrent stroke	0	0	
Immobility-related complication			0.02
Deep vein thrombosis/pulmonary embolism	1	0	
Falls	7	3	
Pneumonia/chest infection/aspiration	13	8	
Urinary tract infection	5	0	
Pressure sore	0	0	
Co-morbidity-related complication			0.34
Myocardial infarction	0	1	
Other*	21	17	-
Any immobility-related complication**	17 (68.0%)	7 (36.8%)	0.01
Any complication	25 (51.0%)	19 (35.2%)	0.11

* Other included a range of different conditions such as chest pain, dehydration and gout.

** One patient may experience ≥1 complication

Immobility-related complications accounted for 68.0% of complications in the SC group and 36.8% in the VEM group. The individual trials both showed a reduction in immobility-related complications at one week with an overall reduction of 73% (p=0.01) (Figure 4-4). The level of statistical heterogeneity between the studies in estimating immobility-related complications was low (I^2 = 13.9%). After adjusting for baseline factors, the risk of experiencing immobility-related complications at one week for VEM patients remained significantly lower than that of SC patients (adjusted OR 0.23, 95% CI 0.07 to 0.71; p = 0.01).

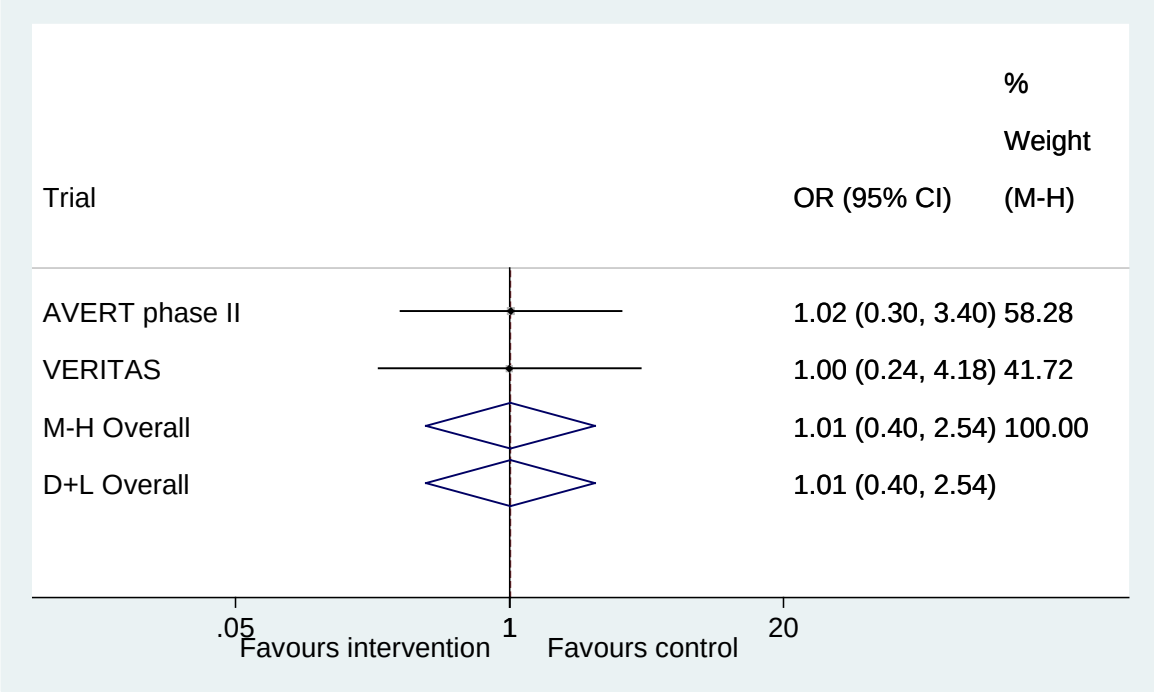
Figure 4-4 Forest plot for immobility-related complications at 1 week



Both trials show a reduction in immobility-related complications at 1 week. Despite being the smaller trial more weight is allocated to VERITAS due to this trial having a higher event rate than AVERT phase II.

The number of patients that experienced excessive fatigue was similar in both groups (VEM = 16 [44.4%], SC = 17 [37.8%]) with this observation consistent between both the trials. No difference between groups was shown in VERITAS with a slight reduction in the odds of excessive fatigue shown in AVERT phase II (Figure 4-5). No statistical heterogeneity between the studies was detected. The odds of excessive fatigue were no higher for VEM patients than for SC after adjustment of baseline factors (adjusted OR 0.79, 95% CI, 0.27 to 2.31; p = 0.67).

Figure 4-5 Forest plot for excessive fatigue at 1 week



A summary of outcomes at one week is provided in Table 4-4. The treatment effect remained unaffected when using a random effects model in all of the analyses. Overall, the levels of heterogeneity between the studies were low, ranging from between 5.7% and 13.9%.

Table 4-4 Summary table of secondary outcomes at 1 week

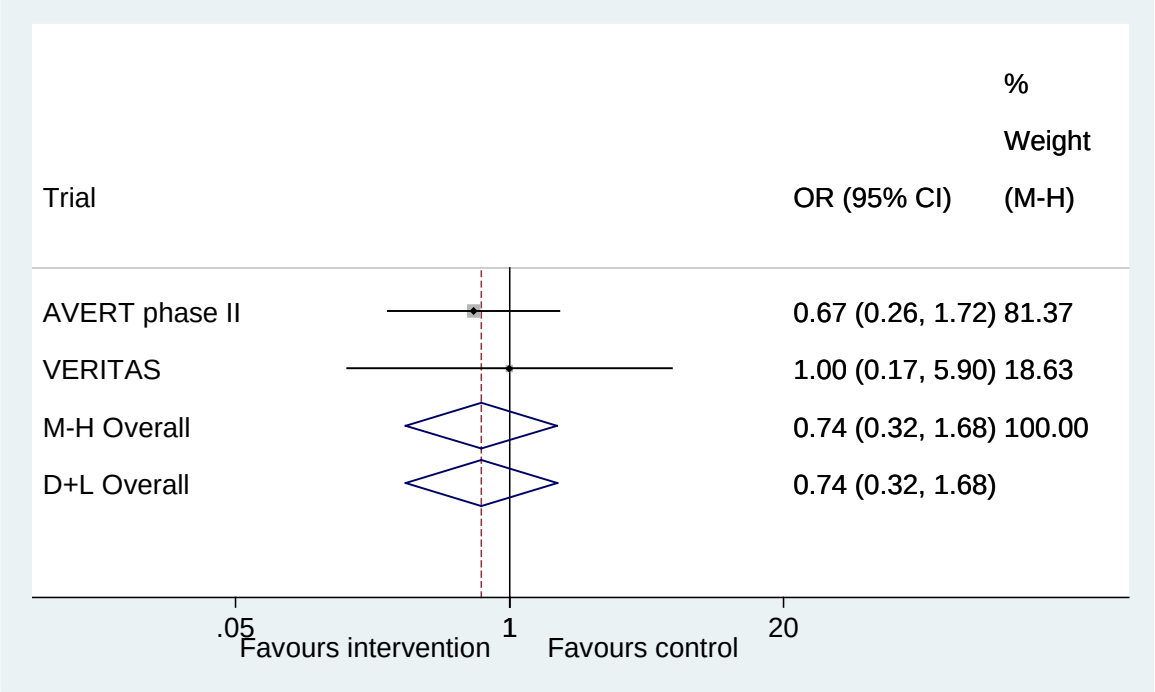
Outcome	Adjusted (Yes/No)	Summary statistic	Summary estimate (95% CI)	p-value
Stroke severity	No	Mean difference*	-0.38 (-3.36, 2.53)	0.78
	Yes	Coefficient	-0.59 (-2.44, 1.27)	0.53
Immobility complications	No	Odd ratio	0.27 (0.09, 0.82)	0.01
	Yes	Odd ratio	0.23 (0.07, 0.71)	0.01
Excessive fatigue	No	Odd ratio	1.01 (0.40, 2.54)	0.75
	Yes	Odd ratio	0.79 (0.27, 2.31)	0.67

* Weighted mean difference

4.3.5 Secondary outcomes at three months

At three months the number of patients in each group that had experienced at least one type of complication further to that experienced at one week after stroke were similar (SC = 61.2%, VEM = 59.4%) (Table 4-5). This observation was consistent between both trials (Figure 4-6) and the effect VEM has in reducing such complications, is reduced (refer back to Figure 4-4). No statistical heterogeneity between the studies was detected.

Figure 4-6 Forest plot for immobility-related complications at 3 months



Immobility-related complications accounted for 66.7% of complications in the SC group and 50.0% in the VEM group. The risk of experiencing complications of immobility in VEM patients was not significantly lower than that of SC patients (adjusted OR 0.55, 95% CI, 0.23 to 1.32; p = 0.20). In summary, the total number (includes all complications at 1 week and 3 months) of patients that had experienced an immobility-related complication in the VEM group was 20 (37.0%) and 21(42.9%) in the SC group.

Table 4-5 Immobility-related complications at 3 months

	SC (n=49)	VEM (n=54)	p-value
Number of patients	49	54	
No of complications			
1	13	17	
2	5	7	
3	4	4	
4	4	1	
5	0	0	
6	3	0	
7	1	1	
8	0	2	
Stroke-related complications			0.60
Death	2	4	
Progression	2	0	
Recurrent stroke	0	1	
Immobility-related complication			0.94
Deep vein thrombosis/pulmonary embolism	0	1	
Falls	21	23	
Pneumonia/chest infection/aspiration	2	2	
Urinary tract infection	10	7	
Pressure sore	1	1	
Co-morbidity-related complication			-
Myocardial infarction	0	0	-
Other*	38	31	-
Any immobility-related complication**	20(66.7%)	16(50.0%)	0.23
Any complication	30(61.2%)	32(59.3%)	0.84

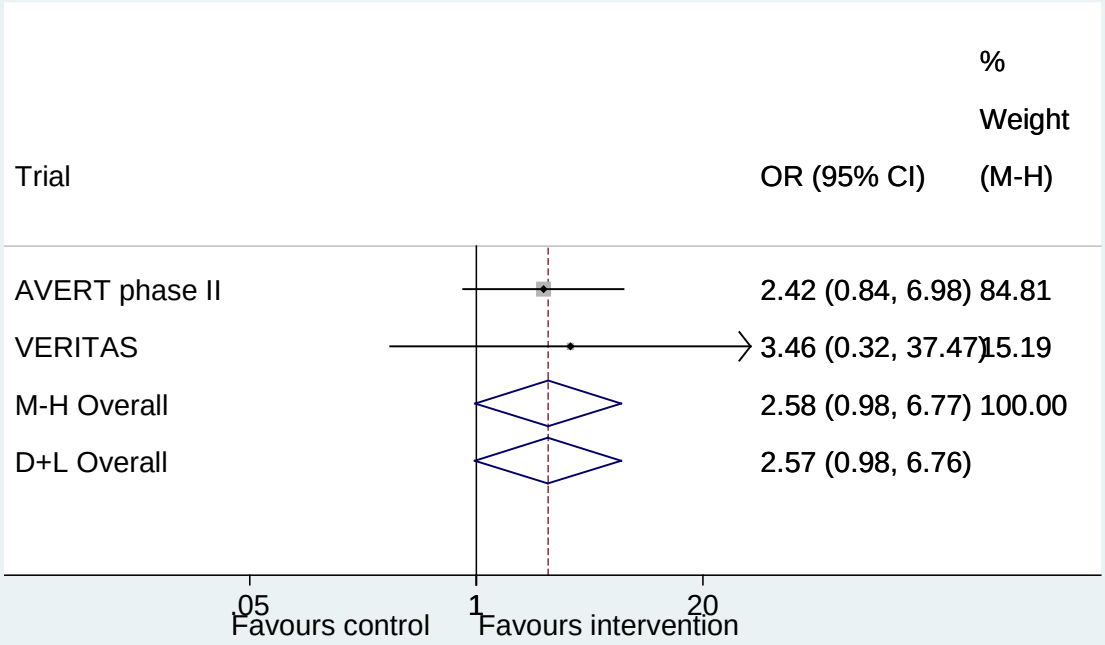
* Other - refer to Table 4-3

** One patient may experience ≥1 complication

At three months the SC and VEM groups had similar proportions of patients living in private residence, a rehabilitation unit, residential housing or a nursing home and are as follows: 67.4% versus 70.4%, 8.2% versus 1.9%, 6.1% versus 3.7%, 6.1% versus 3.6%, respectively. The number of patients that had previously lived in private residence, but at three months had not since returned home was 28.6% in SC group and 22.2% in VEM group. There was no strong evidence that VEM influenced the patients' chances of returning home by three months (adjusted OR 1.40, 95% CI, 0.46 to 4.30; p = 0.55). The level of statistical heterogeneity between the studies in estimating the chances of returning home was low (I^2 = 27.2%). The VEM group had a greater but statistically non-significant number of deaths at three months than that of the SC group (SC = 4, VEM = 8, p = 0.32). The level of statistical heterogeneity between the studies for this outcome was low (I^2 = 28.0%). On multivariate analysis there was no evidence to suggest that VEM resulted in a greater risk of death (adjusted OR 0.93, CI 95% 0.11 to 7.90; p = 0.95). The forests plots for discharge home and death are not shown.

Patients who had undergone VEM had a higher RMI score at three months than patients who had undergone SC practices (median score 6.5 [IQR 1 to 10] versus 5 [IQR 0.5 to 8], respectively). A greater proportion of VEM patients had non-impaired mobility than the SC group (56.0% versus 35.4%) with this observation and a positive effect present in both the trials (Figure 4-7). No statistical heterogeneity between the studies was detected. The pooled adjusted estimate showed that there was a much higher chance of a patient undergoing VEM having non-impaired mobility (adjusted OR 7.81, 95% CI, 1.70 to 35.0, p = 0.01). The wide CI indicates that there is a high degree of uncertainty associated with this estimate.

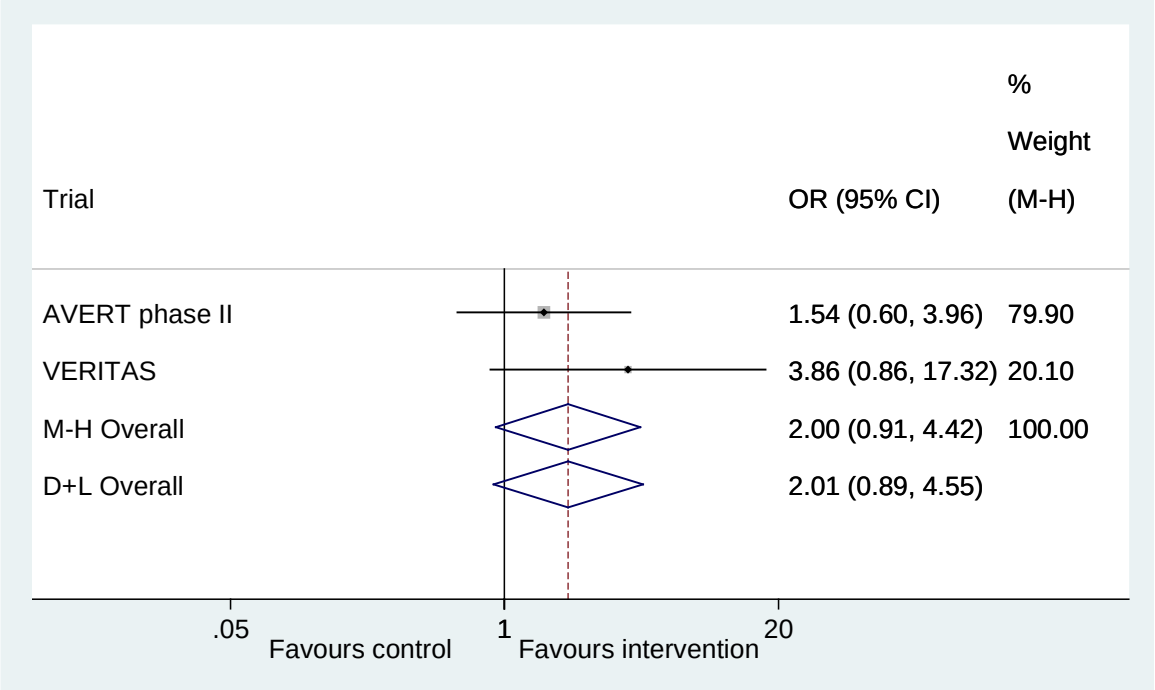
Figure 4-7 Forest plot for non-impaired mobility at 3 months



Very early mobilisation patients had a higher level of ADL at three months than SC patients (median BI scores 20 (IQR 16.5 to 20) and 17 (IQR 12 to 20), respectively. Again, this effect was apparent in both the trials (Figure 4-8). No statistical heterogeneity between the studies was detected. Patients that received VEM were more likely to be independent in ADL at three months than SC patients (adjusted OR 4.20, 95% CI 1.34 to 13.5; p = 0.02). Scores were not

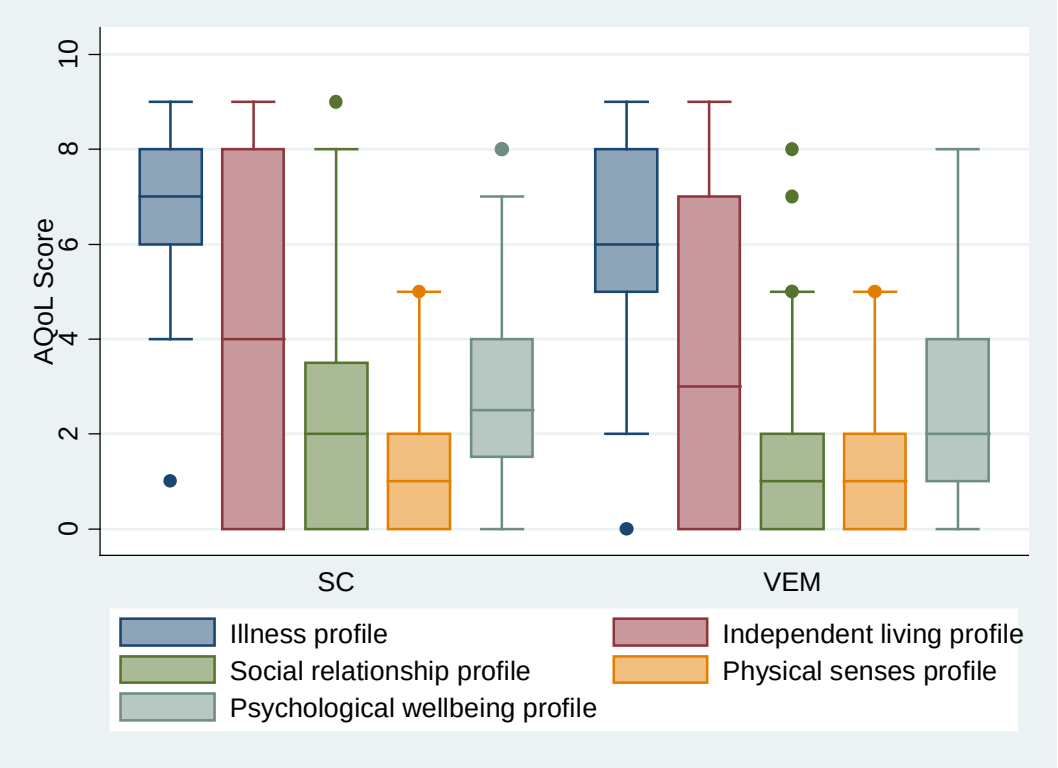
available for two patients; one patient was unable to complete the assessment and one patient was not contactable.

Figure 4-8 Forest plot for independence (BI) at 3 months



A complete set of HRQoL scores for five domains was available for 97(94.2%) patients. Four patients did not complete the questionnaire and two patients did not complete it fully. The median HRQoL score for VEM patients was lower than for SC patients suggesting VEM patients had a better HRQoL (12 [IQR 5.0 to 19.0] versus 14 [IQR 8.0 to 22.0], p = 0.09). To re-cap, scores for each domain range from '0 to 9', where '0' represents 'normal' or 'good' HRQoL and '9' the worst possible HRQoL score. Differences in scores between VEM and SC patients for each of the five domains are as follows; Illness: 6.0 (IQR 3 to 7) versus 6.0 (IQR 5 to 8), p = 0.14; independent living: 1.0 (IQR 0 to 5) versus 4.0 (IQR 0 to 8.0), p = 0.22; social relationship 0.0 (IQR 0 to 2) versus 2.0 (IQR 0 to 3.0), p = 0.05; physical senses; 1.0 (IQR 0 to 2) versus 1.0 (IQR 0 to 2), p = 1.0; psychological wellbeing: 2.0 (IQR 0 to 3) versus 2.0 (1.0 to 4), p = 0.09 (Figure 4-9). Very early mobilisation appears to have the most influence on the social relationship domain, this score being significantly lower for VEM patients than SC patients.

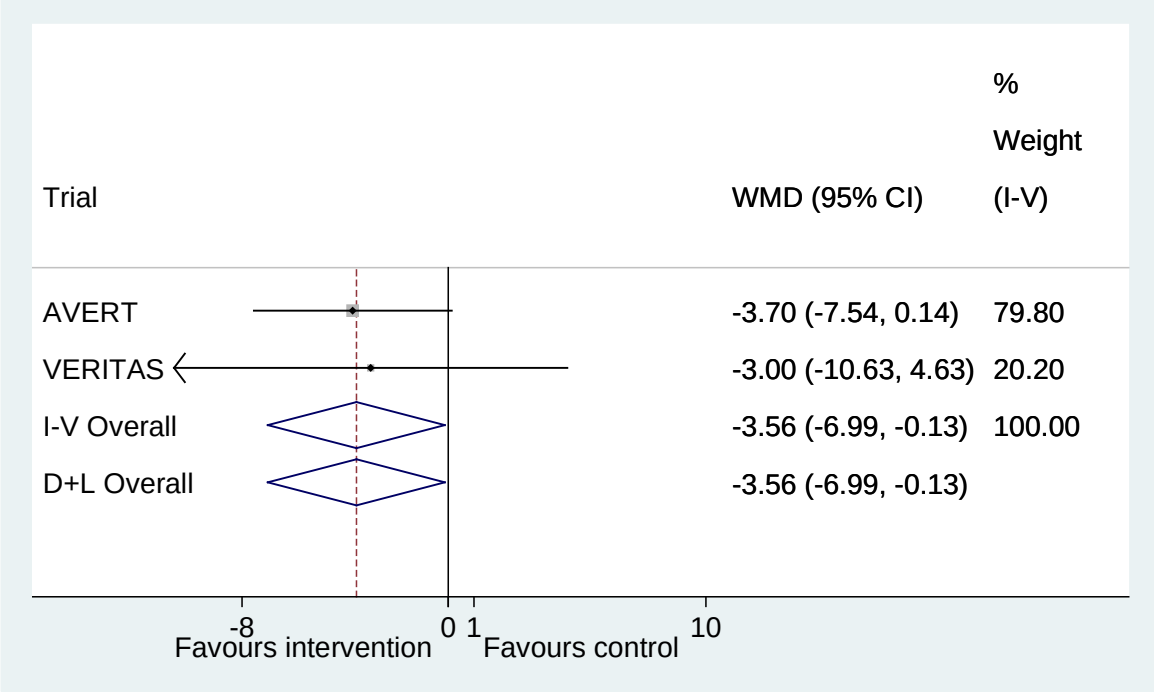
Figure 4-9 Boxplot of AQoL scores for each domain by group at 3 months



Number of patient = 97. Assessment of Quality of Life scores for each domain range from '0 to 9', where '0' represents 'normal' or 'good' HRQoL and '9' the worst possible HRQoL score. Apart from the social relationship profile, there is no or little difference in scores for each of the HRQoL domains between VEM and SC patients.

For both of the trials HRQoL scores were lower in the VEM group than the SC group, resulting in negative difference in means (Figure 4-10). The effect of VEM, after adjusting for covariates was non-significant (adjusted coefficient -3.63, 95% CI -7.30 to 0.13; p = 0.06).

Figure 4-10 Forest plot for HRQoL at 3 months



A summary of the secondary outcomes at three months is provided in Table 4-6. Again, reverting to a random effects model did not alter the estimates in any of the analyses. Overall, the level of heterogeneity between the studies was low, ranging from between 0% to 28.0%.

Table 4-6 Summary table of secondary outcomes at 3 months

Outcome	Adjusted (Yes/No)	Summary statistic	Summary estimate (95% CI)	p-value
Immobility complications	No	Odd ratio	0.74 (0.32, 1.68)	0.47
	Yes	Odd ratio	0.55 (0.23, 1.32)	0.18
Discharge home	No	Odd ratio	1.16 (0.50, 2.66)	0.73
	Yes	Odd ratio	1.40 (0.46, 4.30)	0.55
Death	No	Odd ratio	1.81 (0.54, 6.09)	0.34
	Yes	Odd ratio	0.93 (1.11, 7.90)	0.95
Non-impaired mobility	No	Odd ratio	2.57 (0.98, 6.76)	0.05
	Yes	Odd ratio	7.81 (1.70, 35.0)	0.01
Independence in ADL*	No	Odd ratio	2.01 (0.89, 4.55)	0.07
	Yes	Odd ratio	4.20 (1.34, 13.5)	0.02
Health-related QoL**	No	Coefficient	-3.56 (-6.99, -0.13)	0.05
	Yes	Coefficient	-3.63 (-7.30, 0.13)	0.06

* Activities of daily living

** Quality of Life

Data on resource use during the intervention stage and at follow-up in each of the trials is shown in Table 4-7. The length and dose of VEM intervention provided to patients was not recorded in VERITAS. The acute length of hospitalisation in the VEM groups of both trials was lower; mean LOS 9.8 days (SD 8.0 days) versus mean LOS 8.6 days (SD 9.4 days) in AVERT phase II and mean LOS 10.5 days (SD 4.5 days) versus mean LOS 8.5 days (SD 4.4 days) in VERITAS. Both trials showed that VEM patients had a lower mean bed stay for both the initial hospitalisation and re-admission than for SC patients. Rehabilitation provided to SC patients at home was double that provided to VEM patients in both of the studies. District nursing input for VEM patients was higher in AVERT phase II; it should be noted that resource use in this group was accumulated by one patient. Data for the additional resource use items collected in AVERT phase II revealed that the level of resource use for VEM patients was less than that recorded for SC patients. In VERITAS the mean number of visits to the general practitioner was much the same in both groups while the mean number of visits from informal carers was substantially higher ($p = 0.33$) in the VEM group than the SC group.

Table 4-7 Resource utilisation at 3 months by trial

	AVERT phase II				VERITAS			
Resource item	**SC** Mean (SD)	Number of users (%)	**VEM** Mean (SD)	Number of users (%)	**SC** Mean (SD)	Number of users (%)	**VEM** Mean (SD)	Number of users (%)
VEM intervention, days	7.8 (4.9)	33 (100)	6.1 (4.3)	38(100)	-	-	-	-
Daily therapy time, min	17.3 (3.5)	30 (91)	40.3 (22.3)	37(97)	-	-	-	-
Acute-phase hospitalisation, bed days	9.8 (8.0)	33 (100)	8.6 (9.4)	38(100)	10.5 (4.5)	16	8.5 (4.4)	16
Re-hospitalisation, bed days	7.6 (7.9)	8 (24)	6.5 (7.3)	6(16)	0.9 (1.9)	5 (35.7)	0	0
Rehabilitation or therapy at home, n sessions	17.8 (18.8)	18 (55)	7.3 (5.6)	7(18)	6.1 (8.7)	8 (50.0)	3 (5.3)	5 (31.3)
Royal district nursing service, visits	3.4 (1.8)	5 (15)	12.0 (0.0)	1(3)	0	0	0	0
Home help, visits	4.5 (3.5)	2 (6)	2.5 (2.1)	2(5)	1.6 (5.4)	3(18.8)	15.9 (57.6)	3 (18.7)
Interim care arrangement, bed days	24.0 (33.0)	2 (6)	20.0 (9.0)	3(8)	-	-	-	-
Inpatient rehabilitation, bed days	38.1 (24.4)	21 (64)	32.4 (18.0)	13(34)	-	-	-	-
Outpatient rehabilitation, n sessions	3.4 (1.9)	13 (39)	7.8 (5.0)	9(24)	-	-	-	-
Home modification, n	2.3 (1.3)	12 (36)	2.0 (1.3)	8(21)	-	-	-	-
Adaptive equipment, n	4.1(2.9)	17 (52)	2.3 (1.7)	11(29)	-	-	-	-
Delivered meals, n visits	35.0 (42.2)	2 (6)	46.0 (0.0)	1(3)	-	-	-	-
Personal care assistance, n visits	11.9 (10.2)	4 (12)	5 (0.0)	1(3)	-	-	-	-
Change in accommodation, n	-	5 (15)	-	3(8)	-	-	-	-
Respite care - in home or residential, n	20.7 (22.1)	3 (9)	-	0	-	-	-	-
Productivity loss, h/week	30.0 (10.0)	3 (9)	-	0	-	-	-	-
GP visited, n visits	-	-	-	-	2.2 (2.5)	7 (43.8)	2.3 (5.2)	12 (75.0)
Informal carer visited, n visits	-	-	-	-	6.4 (11.3)	7 (43.8)	69.1 (240.2)	4 (25.0)
Other visited, n visits	-	-	-	-	0.9 (2.6)	2(12.5)	0.2 (0.4)	3 (18.8)

In AVERT phase II the first time to mobilisation from stroke onset was significantly shorter for the VEM group (median 18.1 hours; IQR 12.8 hours to 21.5 hours) compared to that of the SC group (30.8 hours; IQR 23.0 hours to 40.0 hours; $p < 0.01$). Similarly, in VERITAS the time to mobilisation was also shorter for the VEM group (median 27.3 hours; IQR; 26.0 hours to 29.0 hours) compared to SC group (median 31.8 hours; IQR 23.0 hours to 46.8 hours); however, this was not significantly different (Figure 4-11). In AVERT phase II the total dose of mobilisation (defined as therapy time) in the intervention period for the VEM group was double that of SC group (VEM 167 minutes; IQR 62 minutes to 305 minutes versus SC 69 minutes; IQR 31 minutes to 115 minutes; $p < 0.01$). Dose of mobilisation was defined as the mean time spent upright in VERITAS, 61.3 (SD 53.6) minutes and 42.2 minutes (SD 56.7) were observed in the VEM and SC group, respectively. The pooled analysis showed that the time to first mobilisation from symptom onset was significantly shorter among VEM patients (median 21 hours; IQR 15.8 hours to 27.8 hours) compared with SC patients (median 31 hours; IQR 23.0 hours to 41.2 hours).

Figure 4-11 Time to first mobilisation (hours) by treatment group

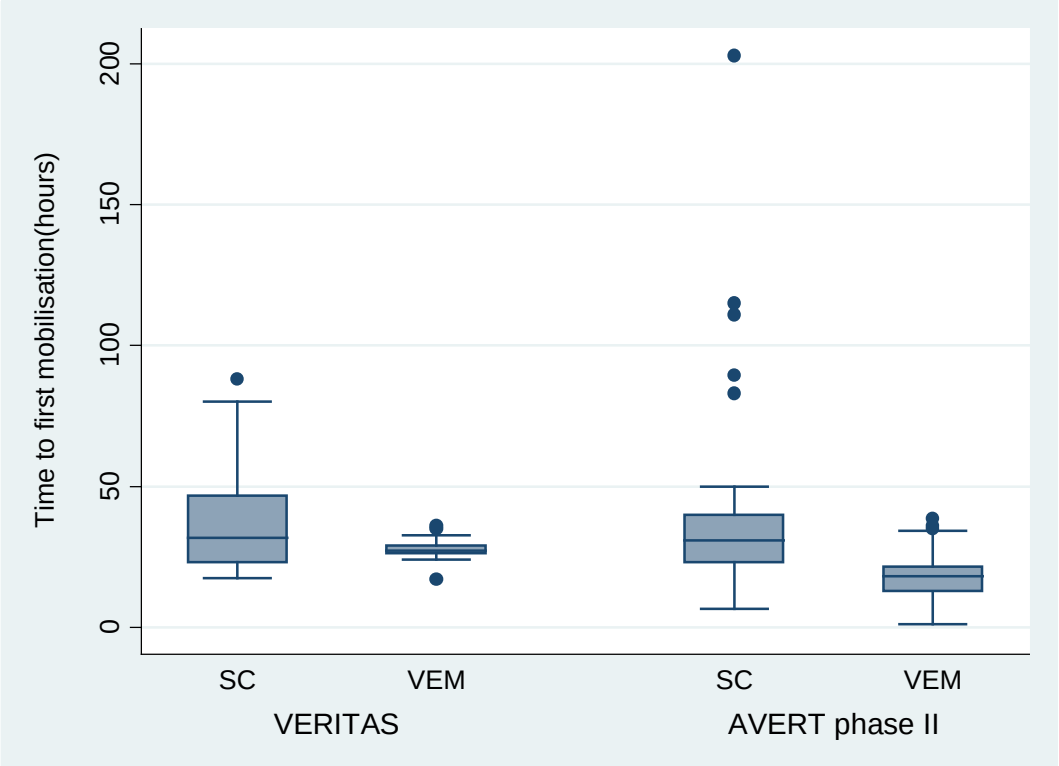
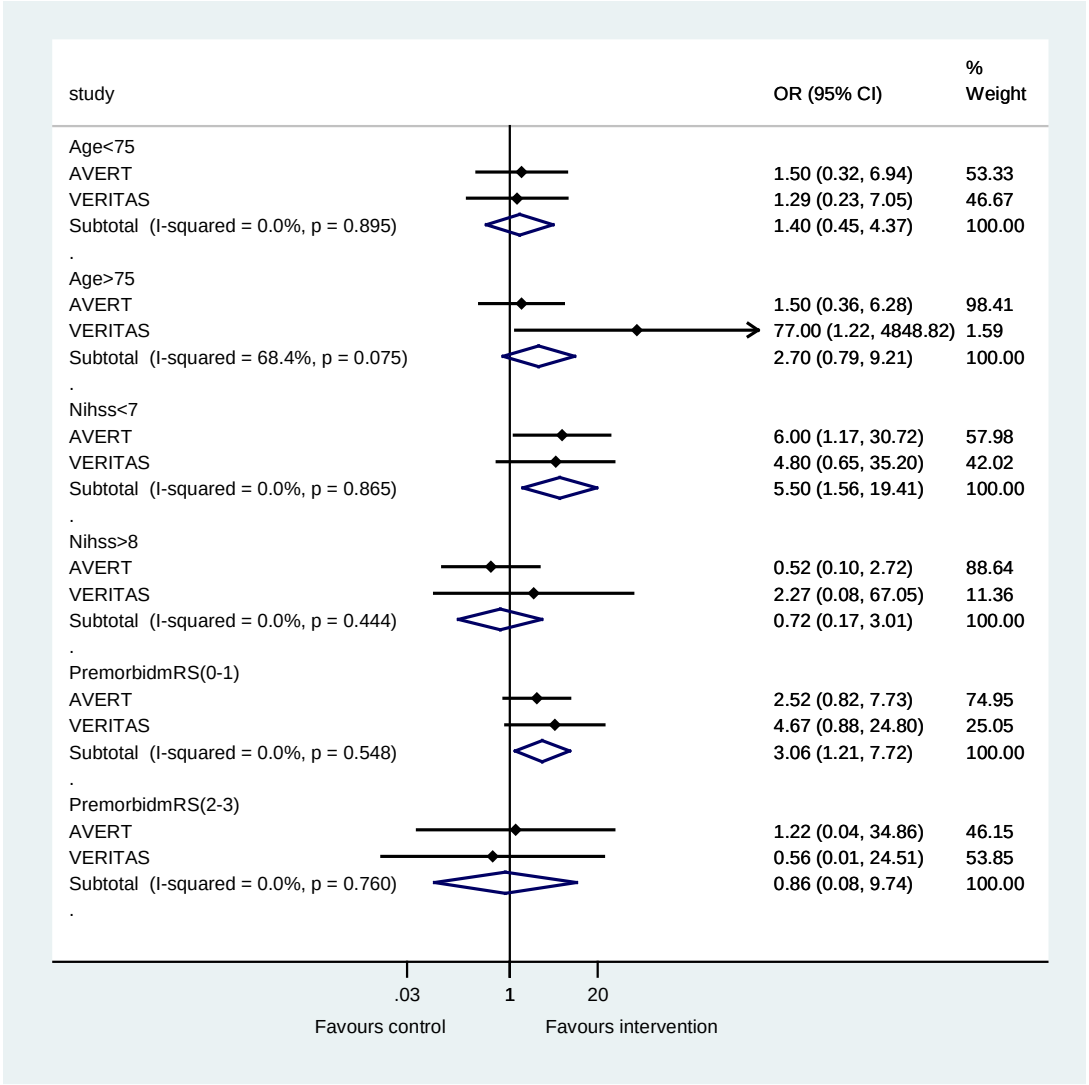


Figure 4-12 displays the stratum specific ORs for each of the predefined subgroups for the primary outcome. There is some indication that some groups of patients may respond differently to the intervention. Therefore, this exploratory analysis supports the need for subgroup analysis to be included in future studies. As with all subgroup analysis, this analysis should be interpreted with caution as it was not sufficiently powered to detect interactions between subgroups. Additionally, the cut-off points were dictated by the small number of events occurring in the pre-selected categories. Reducing information in this way may underestimate the extent of variation in outcome between groups.[158] There was no evidence (subgroup test for interaction: p = 0.59) that VEM was more or less effective for patients aged <75 years (OR 1.40, 95% CI 0.45 to 4.37) than those of >75 years (OR 2.70, 95% CI 0.79 to 9.21). Similarly, there was no evidence (subgroup test for interaction: p = 0.36) to suggest that VEM was more or less effective for patients with a lower pre-morbid mRS score (OR 3.06, 95% CI 1.21 to 7.72) than those with a higher pre-morbid mRS score (OR 0.86, 95% CI 0.08 to 9.74). The analysis by baseline severity indicated a subgroup interaction (subgroup test for interaction: p = 0.04) with a greater odds of independence (with VEM) in the mild stroke group (5.50, [1.56, 19.41]) but not in those with moderate/severe stroke (0.72 [0.17, 3.01]).

Figure 4-12 Predefined subgroup analysis for independence at 3 months



Caution must be drawn when interpreting this subgroup analysis (see text for details). Comparing whether the effect in one subgroup is significant whilst not in another subgroup is not the recommended approach to determine differences between subgroups. It is the overlap of the CIs which indicates statistical significance, but as in Figure 4-12, the CIs can overlap by a small amount yet still have a significant test of interaction.[149]

4.4 Discussion

Summary of key findings: primary outcome

This analysis has shown a favourable effect of VEM in acute stroke patients on independence at three months. By increasing the statistical power and adjusting for confounders known to affect patient outcome in stroke, this analysis has provided a more reliable estimate of effect than previously reported in the

individual studies.[6 7] The notion that beginning rehabilitation early after stroke improves outcome has been examined over recent years with one study showing that early rehabilitation is associated with greater improvement in ADL.[159] A further study showed that earlier admission to rehabilitation is linked to greater functional gains despite functional levels at baseline.[160] These studies compared rehabilitation delivered within a later time frame (within 15 days and within 30 days) than this study which investigates a specific mobilisation intervention within a more acute time frame.

In both AVERT phase II and VERITAS, VEM patients received earlier and more frequent mobility practice than that routinely provided. The treatment effect on the primary outcome in both trials was in favour of VEM suggesting, along with evidence for the use of a fixed effect model (Mantel-Haenszel method), that the individual studies were estimating the same treatment effect. Differences in the size of effect did exist with VERITAS, also the single-centre RCT, estimating a larger treatment size than AVERT phase II. A number of factors could explain this, differences in trial design, study populations and the context in which the intervention was delivered. The treatment effects from single-centre trials are often larger than those produced by multicentre trials.[161] Single-centre trials are associated with having a large treatment effects in meta-analysis, more homogenous populations than multicentre trials and linked to teams highly skilled in the intervention. The single-centre trial in this IPD MA was indeed the smaller of the two studies so may well provide a valid explanation and an important issue to consider when interpreting the results of a meta-analysis.

Summary of key findings: secondary outcomes at one week

Each secondary outcome will be discussed in the same order as presented in the results section. The impact that VEM had on stroke severity at one week was statistically non-significant, suggesting the intervention is not influential in modifying stroke symptoms. Another study which compared mobilising patients out-of-bed at 52 hours with a delayed protocol of mobilisation over six days in acute ischaemic patients showed no significant difference in neurological deficit at day five.[162] The more important implication here is that VEM does not appear to be associated with neurological progression. Patients in both trials who

underwent VEM appeared to have a lower rate of complications associated with immobility. Reduction in immobility-related complications is one of the proposed mechanisms by which VEM may improve outcome.[9] A significant reduction in immobility-related complications was only apparent at one week and when subsequent episodes were considered at follow-up, the effect of VEM seemed to have somewhat diluted. There were some signs of statistical heterogeneity between the trials on estimating this effect. This could be due to differences in outcome ascertainment suggested by the much larger number and variety of complications recorded in AVERT phase II compared to VERITAS. Diserens et al (2012) found no increase in complications, especially severe complications (deep vein thrombosis, pulmonary embolism, pneumonia and acute coronary syndrome) with a protocol that compared mobilisation at 52 hours post-stroke with delayed mobilisation.[162] Fatigue experienced by patients post-stroke is believed to be either alleviated or aggravated by activity. In this study patients who were undertaking VEM were no more likely to report excessive fatigue than SC patients. This has important connotations with respect to implementing VEM whereby HCPs' perceptions of patient fatigue and patient reported fatigue may be a potential barrier to mobilisation.

Summary of key findings: secondary outcomes at three months

Very early mobilisation did not have a significant effect on discharge destination in this study contrasting with previous suggestions that discharge home within 6 weeks is linked to starting mobilisation early in the ASU.[47] The rationale supporting expedited discharge is that patients receiving VEM walk sooner after stroke therefore are more likely to be discharged directly home as opposed to being discharged to a rehabilitation unit.[163] In relation to death, although the number of patients that died in the VEM group was higher, after adjustment for key factors the risk of death was not any higher for VEM patients compared to SC patients. The impact of VEM on death rates along with the other clinical outcomes investigated in this study can only be addressed by a definitive trial.

Patients who underwent VEM were more likely to have non-impaired mobility and independence in ADL at month three. This has important implications considering that regaining independence in activities such as walking after

stroke is thought to be one of the most important rehabilitation goals for patients.[11-13] The CIs around these estimates were wide indicating some degree of uncertainty. Health-related quality of life was higher for the VEM patients than for SC patients. Only four out of 21 studies included in a systematic review (as reported in Chapter 6) showed a significantly different rating of HRQoL in patients who had undergone the stroke rehabilitation intervention under examination than those that did not. Although the instruments used to measure HRQoL were different between the studies included in the review, the domain most affected by the intervention was that relating to physical functioning. In this study patients that had undergone VEM did report a better HRQoL for the most comparable domain - independent living. Scores for the social relationship domain were rated as normal suggesting that patients in the VEM group believed that their health did not impact on relationships nor result in a feeling of isolation. The mean resource use on follow-up tended to be lower for VEM patients than for SC patients and where it was higher the actual numbers of patients using the service was no more than in the SC group. Information about informal care provided to patients after discharge from hospital was collected in VERITAS. This was stated as outwith the scope of study in AVERT phase II. How best to identify and define, measure and value informal care is a challenging area and identified as a shortcoming in many economic evaluations of stroke rehabilitation interventions (as highlighted in Chapter 6).

Summary of key findings: process indicators

Although time to mobilisation was shorter for VEM patients in both trials this was not significant in VERITAS. This may be due to the difficulty in recruiting patients to VERITAS very early after stroke with delayed hospital admission being one potential contributing factor. Not being able to access patients early within a trial setting made mobilising patients more rapidly than usual, challenging. This was particularly relevant for patients most severely affected whereby gaining consent from the nearest relative had further time implications. It should also be noted that once the patient was recruited and randomised in VERITAS there was no delay to commencing the first mobilisation with the time between randomisation to first mobilisation significantly smaller for VEM patients than SC patients. Implementation of the VEM protocol in AVERT phase III

is monitored using data reported by trial investigators about the dose delivered to trial patients. The trial headquarters then assesses these reports against the target VEM dose, as based on the intervention protocol, for that individual patient. Feedback is then provided to the trial investigator to advise them of any shortfall in the intended dose. Albeit, this discussion relates to implementation within the trial setting, if VEM is shown to be effective then the real life implementation of such a policy for patients more severely affected may be compromised. Severe patients are believed to have longer delay in admission to rehabilitation than patients with mild stroke and have a perceived lack of readiness for rehabilitation in the acute stages. These barriers are speculative and may not be restricted to patients with severe stroke. Further exploration of such barriers specific to VEM is required (forthcoming in Chapter 5). Combining data on the dose of intervention delivered in each of the trials was limited by the different methods used to measure activity/therapy in each of the studies.

There were differences in how the intervention was implemented in each of the studies. In VERITAS very early mobilisation was largely nurse-led and was provided for a maximum of seven days (the time period in AVERT phase II was 14 days or until discharge, whichever was sooner). The variation in the providers of VEM and the actual dose delivered in each of the studies could also be used to reason the difference in effect estimated by each of the trials, however is more likely a consequence of the smaller number of patients in VERITAS than AVERT phase II. Also, the majority of patients in the VEM group in VERITAS had a length of stay less than 14 days and in AVERT phase II the VEM intervention was, on average, delivered for six days. A previous meta-analysis investigating different intensities of physiotherapy showed, using sensitivity analysis, that the organisational setting was a factor that influenced outcome and additionally, in support of the previous point, studies conducted in different settings resulted in a smaller treatment effect than those conducted in one setting.[102]

Strengths and limitations

Individual patient data meta-analysis is considered more reliable than a meta-analysis of aggregate data in that it increases the number of participants and often includes more outcomes than that considered in the original analysis. The

exact difference between meta-analyses based on extracting data from the literature and that based on the collection and re-analysing of IPD is not clear. The authors of one study in which a head-to-head comparison of these two approaches was conducted concluded that the results of a meta-analysis based on the literature alone may be misleading.[164] A two-stage approach was used in this analysis as this was considered a more readily interpretable method, providing forest plots to visually assess differences between the studies in terms of magnitude and direction of effect. A post-hoc analysis comparing the unadjusted estimates using the two-stage analysis approach and a fixed-effect regression model gave the same estimate. The use of logistic regression to examine the evidence for subgroup interaction is an alternative test of heterogeneity to that used in this study. The interpretation of subgroup interaction parameters in multivariate models is more complicated. Whether tests for heterogeneity using aggregate data (i.e. Chi^2 test for subgroup interaction) are less revealing than that when using IPD has yet to be concluded. With limited guidance about the most reliable approach to test for heterogeneity between subgroups in an IPD MA, choice may be driven by that more widely adopted and recognised for ease of interpretation.

One of the main limitations of this analysis is the small sample size. The size of the overall treatment effect can therefore only be indicative. Given the small sample size of the individual studies, this pooled analysis should only be considered as an illustration of the method, rather than allowing any confident deductions to be made regarding the effectiveness of VEM. The ongoing AVERT phase III trial will determine the impact of VEM practices using a larger sample. The study samples did vary between VERITAS and AVERT phase III. The patient sample for VERITAS could be viewed as the result of selective recruitment with a low mean age of 65.3 years (SD 11.6), few risk factors for stroke and the majority of patients having mild stroke. The inclusion criteria did not have an upper age limit or restriction on baseline NIHSS score. However, the patient characteristics in VERITAS are largely representative of the local population (registry data, Chapter 2) rather than the result of highly selective recruitment.

Very early mobilisation has remained largely undefined in the literature and distinguishing VEM from SC could prove challenging for some HCPs and is

discussed in more depth in the forthcoming qualitative study (Chapter 5). The IPD MA process of planning, sharing and collaboration in conjunction with the statistical findings from each of the trials provides confidence that the current definition of VEM (and as used in the ongoing AVERT phase III study) is implementable and reproducible in different countries. The opportunity that IPD MA has for demonstrating the replication of an intervention in different settings has implications for the research of complex interventions which traditionally lack definition. The fidelity of complex interventions has received particular attention especially with respect to the flexibility permitted to achieve the desired treatment effect.[28] This is relevant for multicentre trials of complex interventions where the delivering and receipt of the intervention may vary.[30] An IPD MA also offers the opportunity to conduct extensive data checking and the collection of a more comprehensive set of data on all relevant outcomes. Additionally, IPD MA allows for subgroup analysis that otherwise may be limited or not possible if solely based on published summary data from the individual trials. Obtaining and analysing IPD can be both costly and time consuming. In summary, if such practice were to be more widely adopted the process of synthesising the evidence would be more transparent and robust.[14]

The exploratory analysis of specific patient groups provided an opportunity to explore hypotheses around which patients may be most receptive to a protocol of VEM. Knowing more about the patients that may benefit most will assist in the planning of services and the cost-effectiveness of stroke rehabilitation. Using aggregate data from each of the trials a differential treatment effect by stroke severity was observed. Although prespecified, as with all subgroup analyses the finding should be interpreted with caution. Subgroup analysis is not based on randomised comparisons so potentially misleading. The planning and conduct of subgroup analysis should adhere to guidelines.[165] Results from such multiple analyses from studies with small sample sizes are more likely to be chance rather than be a true effect. The number of subgroups used in the analysis was kept to a minimum limiting subsequent false-positive findings (type 1 error) that could be caused by multiple testing. The time horizon available used in this IPD was only three months; recovery may well go beyond this with some patients reporting spontaneous improvements up to and beyond one year post-stroke.

Future use of IPD meta-analysis

There is a current movement towards prospective meta-analysis which identifies studies before any results are released from the individual studies (unlike this, although planned, IPD MA). This approach could overcome some of the recognised biases associated with retrospective (IPD) meta-analyses by pre-specifying research questions, an analysis plan and prospective application of selection criteria. This approach is also more likely to result in the collection of IPD and thus access to data for all patients and outcomes. Prospective meta-analysis also provides the opportunity to ensure that the same outcome measures and definitions are used in each of the studies. The advantage of prospective meta-analysis over IPD MA may be more of a pragmatic one; offering more scope for flexibility in and local ownership of the protocol. This may assist management of the issues associated with intellectual property of protocols between trialists, research institutes and countries.

4.5 Conclusion

This Chapter includes research that addresses the evaluation stage of the Medical Research Council complex intervention framework. When considering the lack of knowledge about the exact components of acute stroke units that are associated with positive outcome, this study has contributed to the evidence-base of one of these key components. It has studied the potential impact of very early mobilisation (VEM) in relation to a number of important clinical outcomes. This analysis approach used has highlighted the value of researcher collaboration with deliberate matching of protocol and outcome measures to allow data from two similar trials of methodological quality to be combined. The results support the need for an appropriately powered trial (the ongoing AVERT phase III) with attention to potential confounders. AVERT phase III aims to recruit over 2,000 patients. The ongoing AVERT phase III follows patients for one year post-stroke and uses inclusion criteria which are generalisable with no restrictions on severity or age. Therefore, VEM can be tested across a spectrum of patient types. This will allow a better understanding of which patients may be most receptive to a VEM protocol.

5 Barriers and facilitators to implementing very early mobilisation

5.1 Introduction

Complex interventions are difficult to implement and the science underpinning the implementation of a complex intervention is not well established.[29 166-168] Implementing new practices into complex health systems poses additional challenges as it may involve collaboration between disciplines or organisational change.[169] For example, aspirin for ischaemic stroke is recommended in guidelines. Achieving this recommendation is multifaceted requiring input from other clinical services to ensure access to a CT scan to exclude haemorrhage, the completion of a swallow assessment and the prescription of the first dose of aspirin. Therefore, although the evidence to support aspirin is undeniable, this guideline requires a careful implementation plan with more than one system and professional group needing to effect a change.[170]

Effective implementation ensures the intervention is workable and integrated in everyday healthcare practice.[31] Embedding qualitative research methods and adopting a mixed method approach are MRC guidelines for the evaluation of complex interventions. A study conducted by Lewin et al (2009) of a sample of RCTs which included qualitative research revealed that the most common methodology, when reported, used ethnography or a grounded theory approach.[171] Most of the qualitative studies were conducted before or during the trial, however there was little attempt to use and integrate the findings of the qualitative study with the results of the main evaluation.

As introduced in Chapter 1 a process evaluation conducted in parallel to a clinical trial allows the opportunity to examine the way in which the intervention under study is implemented during the main evaluation and integrating process data with outcome data allows for better interpretation.[5 30] A number of process evaluations exist in the literature and cover many aspects of implementation such as identifying the factors that may influence implementation, in particular the factors which inhibit the

implementation (barriers) and those which augment the process (facilitators).[172] Barriers can be behavioural, organisational or financial. A lack of time, limited knowledge of the evidence, an absence of institutional policies and inadequate support have all been used to explain poor implementation.[173 174] Factors facilitating implementation have included highlighting the advantages to those involved in the change, encouraging staff to participate in the change process, the presence of a research champion and education for staff.[175] Process evaluations have also aimed to establish levels of satisfaction from those receiving the intervention, to measure implementation fidelity and understand the views of those delivering the intervention.[176 177]

With regards to early mobilisation three studies have previously been conducted to investigate healthcare professionals (HCPs') views of early mobilisation in acute stroke patients. Arias and Smith (2007) conducted a questionnaire study in Scotland which aimed to examine HCPs' views of and knowledge about early mobilisation.[178] This study concluded that staff had a lack of understanding and agreement about the principles of early mobilisation. Skarin et al (2011) and Sjoholm et al (2011) used a nine-item questionnaire to explore HCPs opinions of the benefits and harms of VEM after stroke.[179 180] The main finding was that 60% of HCPs had concerns about early mobilisation, in particular for those patients with haemorrhagic stroke. There were differences in opinion regarding the optimal time point to start mobilisation with 40% in support of mobilising patients within the first 24 hours post-stroke. It included the opinions of HCPs (54%) who worked in other areas other than ASUs. Therefore, the findings of this study may not be entirely representative of the opinions of HCPs currently dedicated to the mobilisation of patients in ASUs. Due to the questionnaire design of the studies the reason(s) why HCPs had concerns about the early mobilisation of acute stroke patients and the differences between professional disciplines could not be fully explored.

The clinical effectiveness of VEM has been investigated in Chapter 4. It showed that VEM has the potential to improve patient outcome at one week and three months post-stroke. However, if the results of the ongoing AVERT phase III concludes VEM to be effective it remains unclear how it will be implemented into routine clinical practice. In the early stages of studying implementation it is

important to understand current practice (problem areas and good practice) and identify potential barriers and facilitators to implementation (evaluation stage of the MRC complex intervention framework, Figure 1-1).

Aim

The aim of this qualitative process evaluation was to identify the barriers and facilitators which may influence the future implementation of VEM into routine stroke care. The beliefs that HCPs hold towards VEM, some of which may act as a barrier or facilitator, were also explored. Beliefs have been defined as 'mental representations of the state of the world'.[181] The wide scope and uses of process evaluations has already been acknowledged. This process evaluation focused on the identification of barriers and facilitators and on gaining an understanding of the beliefs that HCPs have towards VEM.

Objectives

The objectives were as follows:

1. To identify the barriers and facilitators to implementing very early mobilisation in real-life for each stage of the stroke pathway (from pre-stroke diagnosis through to acute stroke unit stay)
2. To identify healthcare professionals' beliefs towards very early mobilisation of acute stroke patients

5.2 Methods

5.2.1 Sampling strategy

Different types of sampling in qualitative research exist including purposive, theoretical, opportunistic and convenience sampling. Sampling in qualitative research is non probabilistic and does not aim to be statistically representative. Instead sampling the units i.e. hospitals and people are selected to reflect particular characteristics of the population with the chances of selection of each element unknown. Purposive sampling, the method of sampling used in this

study, is where the selection of sampling units such as participants or settings is criterion based.[182] These sampling units are chosen because they have certain features which allow detailed exploration of the topic under study. Examples of these features include socio-demographic characteristics or may relate to specific experiences. Decisions around sampling should be based on how broad reaching or rich the data should be. For example, if the sampling is about comparing two main aspects such as male/female and experienced/non-experienced, then it is about generating deep and rich data whilst if the sampling is about getting a range of peoples' views, then it is about generating broad reaching data. The approach to sampling in this study aimed to create both broad reaching and deep data. This allowed the views from different professional groups working in different hospitals to be captured yet allowed for a more in-depth analysis to detect any differences between the HCPs with experience of delivering VEM and the HCPs with no experience of delivering VEM. Therefore, the sampling frame aimed to include a range of hospitals, with and without AVERT phase III experience, from different health board areas (Table 5-1). Only hospital sites in the West of Scotland were included and for practical reasons those outside a feasible commutable distance were excluded. Lewin et al (2009) outlined the advantages of conducting a qualitative study during a trial as having the opportunity to unpack processes of implementation and change and to explore the responses of those delivering the intervention. Given that the AVERT phase III study is ongoing the timing of this study was appropriate and close to the actual event of implementation.

Table 5-1 Factors considered for site selection

Hospital ID	Health board ID	Experience of AVERT	Type of stroke unit*	Feasible commutable distance	Included
1	HB1	×	A,C	✓	✓
2	HB1	✓	B	✓	✓
3	HB1	×	C	✓	✓
4	HB2	✓	C	✓	✓
5	HB2	✓	C	✓	✓
6	HB2	×	C	✓	✓
7	HB3	✓	C	✓	✓
8	HB4	✓	C	✓	✓
9	HB4	×	C	✓	✓
10	HB5	×	C	×	×
11	HB6	×	C	×	×
12	HB7	×	C	×	×

* A: Hyper-acute; B: Acute / semi-intensive; C: Comprehensive

Doctors, nurses, physiotherapists and occupational therapists currently working in the ASUs of the included hospitals (hospital IDs 1-9) were invited to participate in the study. Nursing assistants and therapy assistants were also included. Initial contact was made with the respective manager of each professional group to discuss the research and the practicalities of conducting the interviews. These individuals provided NHS Management approvals for each health board. The nurse unit manager was considered the primary gatekeeper in terms of accessing, identifying and recruiting nursing staff to the study. Therapists and doctors considered more autonomous than nurses were approached directly. All potential participants were issued with an information and willingness to participate form to be returned with their contact details within ten days if they wished to participate. A consent form was signed at the beginning of each interview/focus group. A copy of the information and consent sheets are in Appendix 11 and Appendix 12, respectively. Potential participants had the opportunity to ask the researcher questions during the conduct of the observational study (Chapter 3). As potential participants were aware of the researcher's previous involvement in AVERT phase III in the capacity as Trial Manager any concerns about this research being an attempt to covertly gain 'inside' information on trial conduct were alleviated by explaining the purpose of this research. A student role was adopted which also aimed to prevent participants being guarded about their opinions about the trial intervention and to provide some distance between the participants and the researcher during the interviews. The researcher led all the focus groups and interviews.

5.2.2 Data generation

There are a number of ways in which qualitative data can be generated such as focus groups or individual/paired interviews. Focus groups are a valuable means of gaining insight into participants' perceptions and experiences.[183] Focus groups stimulate interaction and by guiding participants through a set of topics allows the opportunity to observe how issues are conceptualised, worked out and negotiated.[184 185] It was anticipated that the implementation of this intervention would be associated with processes that people do collectively therefore focus groups would provide a means to unravel these activities. Examples of such processes include shared decision making regarding a patient's potential for

mobilisation or staff working together to assist a patient to mobilise for the first time. As VEM is likely to involve a number of different members of the stroke team, each focus group, where possible, consisted of a mix of nurses, therapists and doctors, to capitalise on peoples' different views within a group setting. The group size recommended for a successful focus group ranges from four to 12 individuals to eight to 12 individuals. This study aimed to have focus groups consisting of between six to eight individuals to allow ample speaking time. However, due to the difficulty in releasing staff from the ward to participate in the research, the number of participants in each focus group was actually between three and four. Similarly, difficulties in releasing nursing staff from ward responsibilities to attend a focus group at some hospitals resulted in paired interviews with therapy staff being conducted. Paired interviews proved beneficial in providing more space for thinking and allowing the participants to complement each other's responses and stories.

As a result of the sampling strategy the focus groups/paired interviews consisted of pre-existing groups/pairs which are seen as advantageous in setting a more comfortable scene allowing participants more freedom and confidence to raise sensitive issues or opposing opinions. On the other hand this may also limit groups or individuals who disagree in the workplace with respect to feeling inhibited in the group discussion.

Each consenting participant was provided with written confirmation of the date and location of the focus groups. A reminder letter was sent to the participant by mail or email seven days prior to the focus group. A one page demographic questionnaire was enclosed to be completed prior to attendance. Participants were also provided with a scenario questionnaire which required staff to rate the appropriateness in turn of three different mobilisation strategies for both haemorrhagic and ischaemic stroke. This approach is based on a consensus method known as the 'appropriateness criteria' where different scenarios known to affect decision making around implementing a certain technology are presented. The expected time of completion of these two activities was 15 minutes. It was planned that participants would be provided time at the beginning of the session to complete these questionnaires if need be. This occurred in the majority of cases, with the participants forgetting or having a

"lack of time" to complete the questionnaires. The questionnaire proved to be difficult for HCPs to complete as a stand-alone exercise prior to attending the focus group. Instead, the questionnaire was used as a tool for discussion during the focus groups.

It has often been viewed that involving professionals from different disciplines may potentially inhibit those that are in the company of more dominant professions. Whilst based on the stroke units for the observational study it became obvious that there were differences in practices and opinions between professional disciplines. Additionally, it is recognised that doctors are not actually involved in the conduct of mobilisation, so may have different beliefs from those staff that mobilised patients on a daily basis. Therefore, to ensure professionals felt comfortable during their participation in the study semi-structured interviews were held with doctors as opposed to inviting them to the focus group. There was an opportunity to have informal discussions with nursing assistants about participating in the focus groups. Nursing assistants decided against participation, believing that they would not have anything to offer and that they would feel "uncomfortable" in the presence of trained staff. Due to time-constraints it was not an option to hold separate focus groups for nursing assistants. Nursing assistants were still encouraged to take part and it was emphasised to the nurse manager that these staff members were not excluded from taking part.

An interview schedule was used to ensure that topics were covered in a consistent manner yet flexibility was still allowed. The interview schedule previously used in the Stroke Care Outcomes: Providing Effective Services study was used to inform the questions in this schedule.[186] The interview schedule (Appendix 13) included three main sections:

1. Current stroke service to capture information about the organisation and context of the ward

2. Mobilisation practices to gauge perceptions of very early mobilisation in relation to associated benefits, risks and value

3. Changes that have occurred in stroke care to assess the factors that may influence the implementation of very early mobilisation

A pilot study consisting of one focus group (one nurse and two physiotherapists) was conducted on the 8th October 2010. This hospital (ID 7), was later excluded from the main study. The fluency of the interview schedule was tested, ambiguous questions were identified and the quality of recording equipment was checked. The interview was transcribed verbatim and the responses examined to ensure that the data collected during the pilot met the research aims. The pilot study did not highlight any major concerns regarding the conduct of the interview. Changes were made to the ordering and the wording of some of the questions and the addition of the following question: "Imagine that next week in the unit you had to start mobilising nearly every patient within 24 hours post-stroke what would you need to do this?"

Focus groups were conducted with nurses and therapists between December 2010 and May 2011, in a pre-booked room within or near to the ASU at the staff member's place of work to maximise attendance and situate the participants with familiar and convenient settings. The focus groups were recorded using a digital recorder. An introduction was provided at the beginning of each group detailing the background, purpose and confidentiality of the research. The aim of the study was explained to participants and that this was an opportunity for them to discuss the process of care offered within their units in particular their mobilisation practices. Discussion was facilitated to encourage involvement from all the participants and to probe any responses where appropriate. The focus groups lasted for one and half hours.

Semi-structured interviews were conducted with doctors between December 2010 and May 2011. Interviews were conducted using the same schedule as the focus groups and were semi-structured in nature so as to remain open to discussion beyond the specific interview questions yet maintain focus on the topic.

5.2.3 Data analysis

There are a number of methods that exist to analyse qualitative data such as content and grounded theory which are based on the epistemological (nature of knowledge and how it can be acquired) approach used to address the research question. Content analysis examines both the content and context of data with themes being linked to external factors such as age and gender.[187] Grounded theory develops analytical categories and identifies relationships between them with this process continuing until categories and relationships are 'saturated', and new data no longer contributes to theory under development.[188] Thematic analysis, the choice of analysis in this study, "is a method for identifying, analysing, and reporting patterns (themes) within data".[189] Thematic analysis was seen as an appropriate method to both reflect current stroke practices yet unpack 'the surface of reality'.[189] Framework analysis is a matrix based analysis which allows transparent data management to ensure that all the stages of data development can be systematically constructed.[190]

Immersion in the data was achieved by listening to the interview recordings and by reading the full set of transcripts in entirety and repeatedly. The first three focus groups were transcribed verbatim with the remainder of the recordings being professionally transcribed verbatim. Transcribing provided the opportunity to take an early analytical mind to the data, improve interview style in terms of fluency, to seek definitions and ensure the effective use of prompts in future interviews. Transcripts were checked against the original audio recordings for accuracy. Separate field notes were made throughout the coding process about recurring themes, impressions of the data and questions to follow-up on. Where participants used a particular tone or placed emphasis, annotations were inserted in the transcripts.

Codes were used to categorise similar text together. Thematic coding is a multi-step procedure. Concepts or codes were assigned to the empirical data codes and were initially formulated as close to the text as possible and then became increasingly more abstract.[191] The codes were than categorised into generic concepts and relationships between the categories were developed.[191] There were no restrictions to the number of times that the extracts were coded. The

second coder (NB) read and coded a subset of transcripts. The coding was discussed to define and identify any overlap of codes using the initial version of the coding framework. Thereafter, a second version of the coding framework was devised whereby NB applied this to a different subset of transcripts to test the interpretation of the codes. Barriers and facilitators were identified both directly from the relevant sections of the transcripts i.e. participants responses to question 7 of the interview schedule, and by adopting a more implicit approach. For example, staff when discussing current stroke processes (in response to question 1 of the interview schedule), highlighted how delays in discharge plans impacted on bed availability and thus admission of new patients to the ASU, this was then implicitly coded as a barrier to VEM ('delayed admission to the ASU'). Prevalence data to gauge the importance of each of the barriers and facilitators were not provided (see discussion).

Themes were subsequently developed from patterns in the data such as "conversation topics, vocabulary, recurring activities, meanings, feelings, or folk sayings and proverbs".[192] The transcripts were initially read through to identify emerging and recurring themes. This was an iterative process of arranging codes into broader interpretations, discussing emerging themes and writing up of ideas. Analysis moved from the specific (detailed analysis of each transcript) to the more general (comparing patterns across all the transcripts). The barriers and facilitators that had been identified and coded were interrelated (a facilitator was often the reverse of a barrier) and were more general contextual factors. Therefore, the barriers and facilitators were interpreted together and more broadly within the themes. To represent the keyness of a theme the following terms were used: 'the majority of staff', 'many staff', or 'a number of staff'. The analysis, as well as identifying the themes, also detected differences between professional groups and experiences of delivering the intervention within a trial setting.

The focus groups were analysed in the same way as the interviews, and with particular attention given to the additional aspects that need to be considered when analysing data from group discussion as opposed to individual interviews. These aspects include group dynamics, interactions and the influence of other views.[190] Group dynamics is describing how certain events may affect the way in

which the topic of interest is discussed such as what and how it is said. Interactions are exchanges that occur between group participants to affirm or disagree. The influence of other views is where participants have the opportunity to listen and engage in different viewpoints from others. This allowed the identification of challenges or consensus between participants.

The literature was interspersed with the findings to provide background and to develop theories about the data. The final themes derived from the data were linked together using three headings (specification of the intervention, organisational characteristics and provider characteristics) to achieve a coherent and detailed narrative based on the experiences of the participants. Themes were described under the relevant heading with extracts which best illustrate the theme provided. Descriptors for each extract are provided in parentheses. These include participant ID, profession and experience of VEM ('non-VEM' refers to participants with no experience of delivering the trial intervention and 'VEM' refers to participants with experience of delivering the trial intervention). The 'experience of VEM' descriptor was not applicable for quotes from doctors or from specialist nurses. Where extracts were conversations from paired interviews or focus groups the interview ID (as featured in Table 5-2) was provided under the quote. The term 'staff' is used interchangeably with 'HCPs' and includes all participants. The term 'therapist' refers to physiotherapists and occupational therapists. Nvivo software (version 9) was used to code the data.

5.2.4 Ethics and management approval

Ethical approval was granted by the West of Scotland Research Committee on 8th October, 2010. Research and Development Management approvals were granted on 21st October 2010, 17th January 2011, and 28th January 2011 for each of the three health board areas. Two substantial amendments were subsequently approved; the first amendment was to approve the changes of the interview schedule after the pilot study and the second to approve the use of semi-structured and paired interviews in the study design.

5.3 Findings

5.3.1 Participants demographics

Thirty-one HCPs from seven different hospitals and across three health board areas participated in the study. Four of the hospitals had been previously or were currently involved in AVERT phase III. Several attempts were made to arrange interviews with staff from the other included hospital, however these were unsuccessful. In total, six focus groups and seven semi-structured interviews, three of which were paired, were conducted. All of the focus groups comprised of a mix of nurses and therapists. Two out of the three paired interviews conducted were with two therapists with the remaining paired interview conducted with one nurse and one physiotherapist. The composition of these groups is provided in Table 5-2 along with a full list of participants with focus group/interview ID professional group and VEM experience.

Table 5-2 Characteristics of participants

Focus group/interview ID*	ID**	Profession	VEM experience***
F1	1	Physiotherapist	VEM
F1	2	Stroke Specialist Nurse	NA
F1	3	Nurse	VEM
F1	4	Physiotherapist	VEM
F2	5	Stroke Specialist Nurse	NA
F2	6	Physiotherapist	Non-VEM
F2	7	Occupational Therapist	Non-VEM
F2	8	Occupational Therapist	Non-VEM
Interview	9	Doctor	NA
Interview	10	Doctor	NA
Interview	11	Doctor	NA
F3	12	Physiotherapist	VEM
F3	13	Nurse	VEM
F3	14	Nurse	VEM
F4	15	Occupational Therapist	Non-VEM
F4	16	Occupational Therapist	Non-VEM
F4	17	Occupational Therapist	Non-VEM
F4	18	Nurse	VEM
F5	19	Physiotherapist	VEM
F5	20	Nurse	VEM
F5	21	Nurse	VEM
Interview	22	Doctor	NA
PI 1	23	Physiotherapist	Non-VEM
PI 1	24	Nurse	Non-VEM
PI 2	25	Occupational Therapist	Non-VEM
PI 2	26	Physiotherapist	Non-VEM
PI 3	27	Physiotherapist	VEM
PI 3	28	Physiotherapist	VEM
F6	29	Physiotherapist	Non-VEM
F6	30	Nurse	Non-VEM
F6	31	Occupational Therapist	Non-VEM

* "F" refers to focus group, "PI" refers to paired interview

** "ID" refers to participants individual identification number

*** "VEM" refers to experience of delivering very early mobilisation within trial setting. "Non-VEM" refers to no experience of delivering very early mobilisation.

The highest proportion of HCPs were female and were aged between 31-50 years (Table 5-3). The therapist group (54.9%) comprised of physiotherapists (35.5%) and occupational therapists (19.4%). Two of the 10 nurses were stroke specialist nurses. No nursing or therapy assistants participated in the study. Most HCPs had worked in their current position for less than six years and had worked with stroke patients for greater than 10 years.

Table 5-3 Demographics of participants

Characteristic	Number (%)
Age (years)	
≤30	5 (16.1%)
31-50	22 (71.0%)
≥51	4 (12.9%)
Gender	
Male	4 (12.9%)
Female	27 (87.1%)
Profession	
Doctor	4(12.9 %)
Nurse	10(32.2 %)
Occupational Therapist	6(19.4 %)
Physiotherapist	11(35.5 %)
Length of time in present position (years)	
<6	18 (58.3 %)
6-10	9 (29.0 %)
>10	4 (12.9 %)
Length of time worked with stroke patients (years)	
<6	10 (32.3 %)
6-10	7 (22.6 %)
>10	14 (45.1 %)
Accredited education/training specific to stroke	
No	11 (35.5 %)
Yes	20 (64.5 %)
Experience of VEM	
No	13 (41.9%)
Yes	12 (38.7%)
NA*	6 (19.4%)

* Includes all doctors and 2 stroke specialist nurses not expected to deliver VEM. Two doctors and one stroke specialist nurse worked at hospitals involved in AVERT phase III.

Specification of the intervention

The themes in this category focus on the definition of VEM and if and how it can be distinguished from current mobilisation practices.

The themes that are covered are as follows:

- Defining the intervention
- Accessing patients within 24 hours
- Mobilising patients more frequently

The demands that VEM may have on current stroke processes were explored and the associated barriers and facilitators identified. This allowed the assessment of how congruent the intervention is with current stroke practices.

5.3.2 Defining the intervention

Staff defined their current practice as early mobilisation, believing that they already mobilise patients early after stroke; *"I don't think it's* [VEM] *something that we don't do at the moment"* was the immediate response from the majority of participants. The key identifiers used to differentiate VEM from other mobilisation practices were the 24 hour timeframe of the first mobilisation and the increased frequency of mobilisation practice. Differentiating between current mobilisation practice and VEM was not always straightforward for staff. Staff from hospitals not participating in AVERT phase III interpreted the timeframe as 24 hours from hospital admission to the stroke unit not from the onset of stroke symptoms. In addition, the reliability of determining this timeframe underpinning the intervention was questioned.

> *"…if you try to qualify that then it is a very rare person that you can actually get a true time of onset…its a very very small proportion and a lot of people wake up with strokes…so who knows?..."*
>
> (ID 5, Stroke Specialist Nurse)

The exact reason for adopting this current practice of early mobilisation was not clear, yet, appeared to have been developed via clinical experience and the opinions of clinical leaders, with staff giving the impression that this is just what we do. A recent questionnaire survey revealed that most stroke professionals did not require high-level evidence to justify the need for certain practices such as VEM.[180]

"I know when I was an SHO [Senior House Officer] people did seem to sit around a lot longer, but I'm not sure what their thinking was or there just was no thinking about it. I don't, I don't know."

(ID 11, Doctor)

Occasionally the terms 'mobilisation' and 'therapy' were used interchangeably with staff often correcting themselves as illustrated in the following extract.

"I say therapy but actually it's mobility, it's different. Because therapy is the therapist, mobilities, everyone, so what I mean is they should be mobilised as much as we can all do with them."

(ID 10, Doctor)

Nurses and doctors were the only professional groups that openly questioned what was meant by mobilisation in relation to the intervention:

"What are the mobilisations? if it's a…somebody who is walking with one, you walk to the nurses station and back again, doing that twice a day, then yes, we could do that without additional nursing staff."

(ID 18, Nurse, VEM)

Or whatever mobilisation is, um, as soon as possible."

(ID 22, Doctor)

5.3.3 Accessing patients within 24 hours

Gaining access to patients within 24 hours of stroke onset was the main barrier to delivering VEM identified by participants. Patients were not routinely in the ASU within this timeframe, due both to delayed patient presentation to hospital and delayed diagnosis of stroke (and so a delay in transfer to the stroke unit). The success of the stroke referral pathway was dependent on the individuals operating the system. Adherence to stroke referral protocols and being able to make a rapid stroke diagnosis was heavily reliant on the level of experience the admission staff had in managing stroke patients. Stroke consultants, liaison nurses and managed clinical networks had invested effort, with some success, into making stroke protocols visible and to train front door staff and bed managers about the importance of getting patients with a diagnosis of stroke into a dedicated stroke unit. The system was still prone to delays in diagnosis, inappropriate referrals and break-downs in communication resulting in delayed

admission to the stroke unit.

> *"I think our problem arises more when we actually can't get them into the unit within the 24 hours."*
>
> (ID 19, Physiotherapist, VEM)

Delayed patient presentation to hospital was experienced by all of the hospitals and viewed as out of the control of HCPs expected to deliver VEM. Staff from three hospitals experienced delays in admitting patients to the ASU, often due to the lack of bed availability as a consequence of delays in discharge. Nurse unit managers and doctors negotiated with bed managers, often transferring a patient out of the ASU to make a bed available for a new patient. Staff with experience of VEM overcame this challenge by conducting the first mobilisation for trial patients outside the unit, however, they highlighted that this was for the purposes of a trial protocol. Therefore, this approach would require ward staff to work outside the ASU and therefore could not be easily implemented beyond the trial and into everyday practice.

Even a rapid diagnosis of stroke followed by immediate admission to the ASU may not guarantee mobilisation within 24 hours of the stroke event as it further depended on the patient's time of arrival to the ASU and staff availability. Subsequently the majority of staff questioned the workablility of VEM in routine practice. Some discussion was given to the feasibility of educating staff outside the ASU specifically in VEM, yet there was an appreciation that these non-stroke specialist staff already had a range of medical conditions to manage and related protocols to implement.

> *ID 21: "…if you are educating staff down there in the ARU but stroke is not their priority.*
>
> *ID 20: They've got a lot to do.*
>
> *ID 21: They have so many priorities down there…"*
>
> Focus Group 5 (ID 19 – Physiotherapist; VEM, ID 20 – Nurse, VEM; ID 21 - Nurse, VEM)

Interestingly, out-sourcing the task of first mobilisation was considered to potentially dilute stroke care as a speciality.

"…whereas you know the physio or whoever it is in that ward is not a specialist in stroke, may not be confident, you know, to, you know, to assess and then to get that patient up, erm, so training issues and, you know, do we want them doing that because then is it taking away from our speciality, erm, you know, if they can do it well why do we need to come here, erm, so I guess if we can get them here ASAP, but I don't know."

(ID 29, Physiotherapist, non-VEM)

Alternatively, a doctor suggested that if patients were not getting to the unit in time then an outreach facility to provide specialist stroke input to medical receiving units could overcome these difficulties.

"…um, or, outreach to the receiving units and do more there, um, because at the moment, a large chunk of our patients are still in the receiving unit within that 24 hours – you know, if the guidelines said it had to be within 24 hours, then we would have to raise our game a little bit from that perspective."

(ID 22, Doctor)

Opinions of staff were dependent on the organisation of stroke care within each of the hospitals in which they worked. For one particular unit seeing patients within 24 hours of stroke onset was atypical which made it difficult for staff to even speculate about mobilising patients within this more acute time frame.

R: *"I think going back to what you said really the 24 hours we probably don't get that many people…we do get some but not many so really our answers are a bit flawed…I think we cant really honestly answer.*

I: *But if you could access patients within 24 hours…*

R:*…but you would need to know what there are like in that 24hours and I don't know if the experience is there to know that possibly….do you know what I mean?"*

(ID 5, Stroke Nurse Specialist)

5.3.4 Mobilising patients more frequently

Most staff believed that increasing the level of mobilisation undertaken by patients would be challenging. Once admitted to the ASU accessing the stroke patient in between the routine proceedings of the ward such as ward rounds and protected meal times was considered to be an obstacle to direct patient contact and provision of therapy as practice stands now, let alone increasing

mobilisations. Patients were frequently away from the ward for tests, often staff not knowing exactly what test they were away for and when they were expected to return.

> *"I find the patients' days a pretty well…they're absolutely packed full of stuff because, you know, you can't, you can't go near them when they're eating their meals now…".*
>
> (ID 11, Doctor)

This resulted in failed attempts to access patients throughout the day. In these cases accessing patients was considered to be opportunistic rather than planned, often in parallel with other staff waiting to see the same patient (this is further explored in the "unpredictability and planning" theme).

> *"…and probably more often than not therapists want to see them at the same time as well, so, you know, it's just trying to fit in your timetable with patients as best as possible".*
>
> (ID 30, Occupational Therapist, Non-VEM)

Organisational characteristics

The themes within this category describe how characteristics of stroke units may affect the operationalisation of VEM. The themes that are covered are as follows:

- Environment
- Unpredictability and planning
- Teamwork
- Resources
- Time
- Evidence-based practice
- Organisation norms to change

Staff perceived a need for additional resources to support VEM and that the collective contribution from the MDT and the enrolment of key players such as hospital managers for the successful implementation of VEM. The usefulness and effectiveness of implementation strategies such as champions are discussed and illustrated using other acute stroke interventions recently introduced to the hospitals.

5.3.5 Environment

Participants described the ambience of the units in a positive manner, with staff taking pride in what they do and the staffing structure frequently referred to as non-hierarchical; as one HCP noted *"everyone speaks to everyone"*.

> *"I think that most staff are positive about their jobs on the unit. Obviously I can only speak for myself but I enjoy coming to work and when you come in it's a friendly atmosphere and I get the impression that everyone else actually enjoys being here and working because everyone puts in maximum effort."*
>
> (ID 6, Physiotherapist, non-VEM)

The atmosphere in the stroke units was distinguishable from that of other specialities mainly due to the noticeable respect that staff had for each other's roles, MDT working and the shared decision making. Participants believed that everyone's opinion was valued unlike other departments where, for example, occupational therapy was viewed as a tick box exercise.

> *"Because you see a different respect for the medical staff as well and they, they very much respect everybody in the team here, it's not the case that I'm God, what I say goes, it's not like that. We respect everybody's opinions and I think that's a big, big thing."*
>
> (ID 21, Nurse, VEM)

The physical layout of wards was not seen to be conducive to patient mobilisation. The general design of hospital wards and in some cases unattractive facilities did little to encourage patients to mobilise beyond the bedside or from the ward to other areas such as dayrooms.

> *"It's too far to walk to the toilet, so actually they, they've got no opportunity to do any additional mobilisation".*

(ID 19, Physiotherapist, VEM)

Lack of space was a big issue especially in terms of therapy and areas around the bed space making it cumbersome and time consuming to assist a patient out-of-bed. Staff competing for space with other members of the team and using spaces not intended for therapy was a frequent occurrence. A lack of quiet areas and privacy was a feature common to many of the wards. Dedicated therapy staff having offices and therapy rooms located near to or on the stroke unit was viewed favourably in terms of being able to communicate easily across disciplines.

"So yes, I think obviously as a team that works quite well, probably because, like you're saying as well, that we are kind of close in vicinities to one another; it's not like we're in another part of the building, so you're having to try and trace us down to find things out. That works quite well, it works well in every unit where everyone's based."

(ID 30, Occupational Therapist, non-VEM)

5.3.6 Unpredictability and planning

The medical condition of a stroke patient was viewed by staff as unpredictable with improvements or deterioration evolving quickly and unexpectedly requiring staff to take immediate action and taking precedence over what they were currently doing or planning to do. Constant assessment by the individual HCP and the team was as an aspect of care that staff frequently referred to, ensuring any changes were detected early and acted upon. As already noted, issues such as not knowing when a porter was going to arrive to take a patient off ward to attend a medical test contributed to this unpredictable environment. This required nurses and therapists to have a flexible approach to change their plans.

"You might have a plan in your head as to where you want to go but then that day it might not be appropriate you know to take them up to the kitchen or something because they are not well enough, they have had a bad night or something or it really varies you have to be quite flexible to change your plan quite quickly depending on the outcome of the meeting in the morning or during the day how the patients are."

(ID 8, Occupational Therapist, non-VEM)

In addition to this unpredictability, HCPs had to contend with the variable nature of stroke. Most staff emphasised that the effects of stroke differ

markedly between patients in relation to the level of impairments and disabilities, rehabilitation requirements and responses to treatment. Therefore, to assess the appropriateness of VEM these patient factors would need to be assessed on an individual basis. This made it difficult to provide opinions about the general appropriateness of getting patients up earlier and more frequently. The recovery pathway for patients post-stroke was viewed as uncertain, often ambiguous with differences in opinion existing, in particular around the maximum time horizon for recovery. Nurses believed doctors focused on a three month time point while they, along with therapists, believed that the timescale for recovery was closer to one year. Staff also accepted that stroke patients may well have unexpected outcomes.

> *"We've had people that we just didn't think would do at all* [well] *and…Aye,* [it may end-up that patients unexpectedly] *walk out. Maybe with a Zimmer right enough…"*
>
> (ID 12, Nurse, VEM)

A ward timetable, prepared one day in advance, was used at one of the hospitals to provide structure to the daily organisation of the ward. The timetable allowed the medical tests, therapy or dressing practices that the patient was scheduled for that day to be highlighted. This informed ward staff when the patient was likely to be off the ward providing an opportunity for staff to plan and time manage more effectively. It did not prove popular with staff from hospitals not currently employing such a system, believing that the unpredictable nature of the ASU would make it difficult to apply such a timetable.

> *"In acute, when they're moving as quick and it's really hard to then kind of make a timetable up even for the day, because things can often change pretty much all the time in your day as well, so there's a lot of things going on."*
>
> (ID 31, Occupational Therapist, non-VEM)

One doctor believed planning between physiotherapists and nurses was pivotal to integrating more mobilisations into the patient's day. This doctor was new to the working of this particular stroke unit and may not have been fully aware of the detailed daily communications about the plans for the patient's day that were frequently mentioned by some nurses and therapists at this same hospital.

Nurses and therapists communicated routinely in the morning as a way of receiving an update on new patients, any changes in a patient's condition and to be informed of, or co-ordinate the patient's schedule for the day. This resulted in more effective use of time, for example organising the transfer of a patient who was scheduled for a medical test that day.

> *ID 3: "The other thing that influences it is what investigations they are undertaking….obviously they have just been admitted and they have come in the last few days and they have a lot of investigations to get done and sometimes 'Mrs so and so is going for a scan and she will be going in a trolley so lets not get her upright now lets wait till she has been for a scan and get her up later'*
>
> *ID 4: Or we will get her up and put her back to bed."*
>
> Focus group 1 (ID 3: Nurse, VEM; 1D 4: Physiotherapist, VEM)

5.3.7 Teamwork

Getting the patient out of bed for the first time involved a team approach to assess the patient's suitability for mobilisation, delegate the appropriate professional expertise and to risk assess. Staff stated that the MDT was a key aspect of stroke care. Although not specifically asked to define MDT working it included references to role definition, shared decision making, joint assessments and communication between different professional disciplines and patients. There was trust and respect for each professional group's experience, competencies and perspective.

> *"I would probably get a patient to the edge of the bed, but I wouldn't try and stand them, but I would do that if I was wanting to see what their balance and things was like, but obviously you probably, you know, liaise with the physios as well, just about what, you know, from a therapy point of view where we're at should be similar but different perspectives really".*
>
> (ID 31, Occupational Therapist, non-VEM)

Staff acknowledged that although they were quite often on '*the same page'* it was the ironing out of disagreements to achieve a consensus which demonstrated the strength of MDT working. One example frequently used to illustrate MDT working in practice was discharge planning.

"No, I think we do kind of all come and ask each other before we send, maybe bar some people… but people home and things too; you know, we go round everybody rather than… it's not one person's decision, it's definitely a team decision."

(ID 30, Nurse, non-VEM)

Methods of communicating a patient's level of mobility amongst the stroke team included MDT meetings, written patient notes, bedside mobility charts and morning meetings. All units had at least one main MDT meeting a week where information about patients was exchanged and despite daily communications, were still viewed to be the place where key decisions were made. Nurses viewed these meetings as a landmark in the week in terms of getting information in place before the meeting and ensuring they had a good grasp of the patient's medical history and expected care pathway.

"…or we have a plan, as you say, and sort of say, 'Well, I'm going to take them on stairs today.' And then the OT is saying, 'Well, I'm going to do access visits', so you're kind of ahead of the case conferences. They're (the doctors) wanting answers at the case conference, not a, not a big debate, do you know. They want answers about, do you know, can they go, are they going with [care packages]…what is it they're going home with?"

(ID 12, Physiotherapist, VEM)

Daily communication amongst the members of the MDT was an integral part of stroke care and often starting with mini-MDT exchanges first thing in the morning (between nurses, therapists and, depending on the hospital, medical staff), during ward rounds (nurses and medical staff) and after ward rounds (nurse and therapists). Morning mini-MDT meetings in the majority of units had evolved over time whilst other units had deliberately introduced them. With immediate updates about new patients or changes in medical or mobility status they were seen to have several advantages such as mobilising new patients quicker or expediting discharge.

"…I think the HP staff come in and out a bit, and I think there is a…quite a lot of changing over because…to cover leave, so it's more I think just so everyone gets a chance to know who's about and what's going on, to flag up problems, perhaps to try and move discharges on a bit quicker, perhaps to try and get people mobilised a bit quicker. didn't always have medical input at this which was OK for some patients but not for others."

(ID 11, Doctor)

Communication was not always seamless and a break-down in communication between nurses and therapists, as a result of MDT meetings often having no representation from nursing staff, caused particular tensions in the atmosphere and ward standard practices not being adhered to.

I: *"So sometimes you'll go and the patient's already dressed?*

R: *Sometimes, 90 percent of the time, other than sticking a flashing neon light on the poor patient's head to say for 'dressing practice', I don't know how we're ever going to overcome it. I've been in this ward for eight years and I still can't get dressing practices."*

(ID 25, Occupational Therapist, non-VEM)

Joint assessments between physiotherapists and occupational therapists were beneficial in avoiding duplication in assessments, prevent patient fatigue and to assist mobilisation of a more severely affected patient.

"…we might want to do joint work together, because we're doing some similar things, but the patient may not be able to kind of, erm, tolerate two different sessions, so again it's like kind of communicating that way."

(ID 31, Occupational Therapist, non-VEM)

5.3.8 Resources

Staff agreed a static base of HCPs trained specifically in stroke care was one of the strengths of their units. Most staff believed current staffing levels were adequate enough, yet, operated on a fine balance with staff deployment to other areas, illness or leave having an immediate and obvious impact on the ward. Participants, regardless of their experience in AVERT phase III, when asked what they would need in order to implement VEM in real-life, most frequently stated that they needed an increase in the number of ward staff. The majority of nurses and therapists did not routinely see patients within the first 24 hours of stroke onset so limited by experience hypothesised that higher levels of dependency in this acute timeframe would require more staff to assist in the first mobilisation. There was agreement from all HCPs that to deliver an increased daily level of mobilisations to patients would certainly require more staff.

"Also the early stages that you are probably talking about more staff again, if the person is more dependent at that stage then so, and you're doing that maybe throughout the day which could be four, four times or so during the day if they're able, so, you know, that staffing you literally would have to have staff there in, in those units to be able to, to do that, that are specially trained to do it."

(ID 31, Occupational Therapist, non-VEM)

There were uncertainties associated with this requirement. Firstly, it was unclear what form these additional resources would take. Respondents found it difficult to speculate what type of worker would be required and how many additional staff members would be required to support VEM.

"Yes, yes, if you, if you've got quite a lot of dependent patients and you've needed two therapists per patient, or not even therapists, maybe even like assistant staff for technical instructor staff, and then you could potentially need another kind of one to two of each discipline"

(ID 29, Physiotherapist, non-VEM)

Secondly, how these additional resources would be allocated and utilised. The changeability of the types of patients in the unit at any one time in relation to dependency levels and the number of patients for VEM may pose problems.

"So you can't actually, there's no point in having an extra member of staff on, because……it might, it might be two weeks before you need them the next time."

(ID 22, Doctor)

This need for additional staff to support the implementation of VEM was compared to the staff requirements required to deliver another acute stroke intervention (thrombolysis). As opposed to requiring an increase in nursing levels, staff revealed that thrombolysis was achieved within the current staffing compliment.

"You can't have that kind of resource fail, so it's just done within the complement, but most of the time, that doesn't seem to be too much of a problem, and the staff have been very good actually, because, for instance, if somebody gets thrombolysed late evening, and there aren't enough staff over the night shift to cover, the day staff stay on."

(ID 22, Doctor)

The current focus regarding staffing for nurses was more about reinstating reduced staffing levels to their previous compliment rather than increasing them for the purpose of mobilisation, putting recent financial cuts to staffing budgets into perspective.

> *"We're already at the kind of, we've… our numbers have dropped even further, so we're at the point just now where we're trying to push it back up to where we were before. Erm, I still don't know that that would follow all that… again, maybe with therapists in at the weekend, that would help us slightly, maybe; I don't know."*
>
> (ID 30, Nurse, non-VEM)

Staff were aware that while increasing staffing levels would facilitate the delivery of more frequent mobility in the current economic climate of limited resources felt that this was unlikely to happen. Alternatively a more flexible shift pattern for therapists without necessarily increasing staff numbers was suggested. For example, having a back shift to extend the therapy working day would provide a means to support the mobilisations of patients later on in the day.

> *"Erm, you know, if they've got up in the morning, done well, gone back to their beds again, there's no reason why they couldn't be getting up again...So, again, staff working twelve to eight as well..."*
>
> (ID 27, Physiotherapist, VEM)

This would provide therapists with a broader perspective about the patient's mobility and function across the day. The nursing perspective of how a patient was mobilising can be quite different from what the therapy staff may see at selected points in the day i.e. transferring patients back to bed in the evening can be quite different from getting them out of bed in the morning. The majority of staff felt that VEM would require more equipment including specialist stroke chairs, hoists and hoist slings. In some instances when a particular type of chair was not available a flexible approach to alternating seating so as not to prevent the opportunity to get a patient up sitting out-of-bed.

"Er hoists. There's only one hoist on our ward at the moment [voices overlap] so we would need more maybe handling equipment."

(ID 17, Physiotherapist, non-VEM)

At one hospital, one participant believed that it was the lack of equipment that could pose problems, however another participant viewed a lack of storage as the problem. The data from this focus group is presented below and highlights the strength of the focus group data to provide the opportunity for participants to disagree or provide an alternative viewpoint.

ID 7: "Sometimes we have an issue about appropriate seating in the ward…well not often….but on occasion you don't have enough stroke chairs or enough chairs that might be ideal for the patient so we work round that and modify that and swap seating about and things…but there an abundance of that…

ID 5: I would qualify that by saying that we have actually had the chance to a lot more equipment but our problem is that we have no where to store it and following the health inspectorate we even had to move stuff that we had stored…"

(Focus group 2, ID 5: Stroke specialist nurse; ID 7: Occupational therapist; non-VEM)

Providing therapy cover at weekends was a recurring theme raised by all professional groups, although this did not meet with much enthusiasm from therapy staff. Therapy cover was seen as a facilitator to VEM but also had other advantages by reducing the pressure on the nurses at the weekends and preventing the backlog of new patients to be assessed at the beginning of the week.

"You would think the ward was quiet at the weekend but it's busier because the patients aren't getting any of the OTs or physios so they are, there are more, they need us more. So we don't get as much time at the weekend as we would do during the week to maybe mobilise them as well."

(ID 13, Nurse, VEM)

Therapy input at weekends is traditionally provided to patients considered to be at risk of respiratory problems or requiring input prior to discharge. For one unit the physiotherapists had recently secured a priority system for patients to be seen on public holidays. This was an isolated case and an evidence-base for VEM

was seen as one way in which stroke patients would be prioritised for such a service. Staff were uncertain how this would be funded.

> *"…if anyone in our ward had a respiratory problem that we wanted weekend cover for that (respiratory care) would be fine, erm, but not for, not for mobilisation, not for any kind of rehab issues, erm, but as you say, orthopaedics do, and that comes out of orthopaedics budget, erm, so I don't know if that would be, you know, whether it would come out of stroke budget erm, in, in the future that's how they would get."*
>
> (ID 29, Physiotherapist, non-VEM)

Employing a more flexible approach to therapy working hours may accumulate to a six or seven day working week for therapists. Reducing working hours for therapists Monday to Friday could create scope for therapy weekend cover without having to increase the number of staff.

> *ID 28: "Yeah, but they could take a wee hour off every day, you're working Monday to Friday to… make a wee shift on Saturday… and Sunday.*
>
> *ID 27: I think even a six day service would be* good…
>
> *ID 27:…because I think everybody does need a rest, but it could be a staggered, somebody gets their rest on a Wednesday."*
>
> Paired interview ID 3 (ID 27 - Physiotherapist, VEM; ID 28 - Physiotherapist, VEM)

5.3.9 Time

Lack of time, competing demands on time and the length of time that it took to do certain tasks was frequently mentioned by nurses and therapists. Nurses and therapists valued being able to spend their time equally amongst patients on the ward. Time could easily be absorbed by one patient i.e. a patient with dementia, a particular task or by a patient unexpectedly scheduled for discharge that day.

> *"…between my home visit and my home visit report, ordering equipment and organising things, that's pretty much one patient has taken a big chunk of my day, you know, so then you've got to prioritise the other patients for therapy as well and the new patients, like you're saying that's been in, that need assessed, so there's a lot of kind of flexible planning within that."*
>
> (ID 31, Occupational Therapist, non-VEM)

Therapy sessions for stroke patients were viewed to be more time consuming than that of other patients with one physiotherapist explaining the length of time to prepare a patient for the core therapy session.

> *"And the length of time of taking the patient from the ward, through getting them transferred onto the plinth, doing your therapy and getting them transferred back and taken through to the ward and back in that, you know, a half hour session doesn't warrant for all those things, so sometimes you have to expand your length of session; but as you say, [that could impact on] other patients that you're seeing."*
>
> (ID 27, Physiotherapist, VEM)

Such experiences may have resulted in the nurses and therapists belief that a lack of time would impact on the potential to increase the frequency of mobilisation being provided to patients. Most staff with experience of VEM explained the challenge to deliver the extra mobilisations to patients.

> *"And then there's lots of other things going on, do you know, they've gone for a shower, they've gone for a CT, they've gone to OT, they've gone...do you know. So actually then physically it's very hard for us because there's not enough time in the day to keep going back to them, and then when you go and if you can't get into that one then you think, sugar! So...and it's staffing. We've just had an AVERT patient and it's been a challenge."*
>
> (ID 12, Physiotherapist, VEM)

Very early mobilisation was clearly associated with an increase in workload. One physiotherapist believed the decision to participate in AVERT phase III was reliant on staff preferences for and attitudes towards the intervention and that this association with an increase in work was invalid.

> *"Erm, you know, and I think that kind of sums it up, I just don't think they [referring to the nurses] wanted to do it, I think..... they just saw it as work..... and they didn't get the fact that actually they weren't doing that much work and it was a massive opportunity."*
>
> (ID 27, Physiotherapist, VEM)

Nurses believed that changes over time that have occurred in care now impacts on the time that they can spend directly engaging face-to-face with patients. Therapists prioritised the use of their time, aiming to see more independent patients or patients with low exercise tolerance early on in the day and new patients before morning MDT meetings.

"Yeah I mean we do negotiate, people have got poor exercise tolerance and if we know that [name of Physiotherapist] like bringing them in here at half past ten in the morning…And we know that if we get them up at eight o'clock in the morning, by the time she comes to them, they're going to be fast asleep, then no, we're good at negotiating that and we'll say oh that's fine, we'll keep them in bed and [name of Physiotherapist] will then just get them up and bring them straight through in here."

(ID 18, Nurse, VEM)

Whilst most stroke units operated a 'blanket referral' system for physiotherapists, nurses would also highlight patients to physiotherapists especially about patients they were keen to see mobilised sooner rather than later. For example, this often led to a new patient having priority before a morning MDT so that the physiotherapist after their assessment could feedback at the meeting with regards to patients' levels of mobility. In some cases this facilitated discharge planning. The length of time since stroke onset was not a factor that staff considered when deciding whether or not to mobilise a patient. Staff did not express a need to know an optimal time to mobilisation from stroke onset. Staff revealed no hesitancy in mobilising a patient very early on after stroke as long as they were "medically stable".

5.3.10 Evidence-based practice

Staff considered early mobilisation as an important aspect of stroke care and were aware of its presence in stroke guidelines. Positive results from AVERT phase III could promote the profile of VEM practices within hospitals and capture the attention of hospital managers.

"… and say this has been proven, this can get your patients better results, it can maybe get them faster results but generally better quality of life because I mean it's, I suppose you're thinking about recurrent admissions as well, your decrease in that so I think it would give an awful lot of clout to be able to say money needs to be spent on, or directed [laughing]…into providing… staff to provide that, eh, the early mobilisation, because I think just now it's very hard to go and say, yeah, we think early mobilisation works but they're looking for the hard facts, so… we are kind of keeping our fingers…crossed for AVERT."

(ID 27, Physiotherapist, VEM)

A protocol was seen as one way to facilitate an evidence-based approach to VEM into real life clinical practice. There were a few throwbacks associated with

protocols including the pressure on staff to gravitate away from clinical judgement and as well as providing a reason to do something protocols may also provide a reason for not doing something.

> *"I think I do worry that, you know, it will eventually get to the stage where we are taking away people's own clinical judgement around things, you know, if we start saying well, you know, you'll have to do, you do 20 minutes, three times a day and that will make them better and I suppose if they've got good evidence to prove it then…you would need, you know, if we were working as an evidence based service and whatever then, you would need to do something about"*
>
> (ID 19, Physiotherapist, VEM)

In the following extract, albeit within the context of AVERT phase III, a physiotherapist illustrates that clinical decision may well take precedence over adherence to a protocol.

> *"Do you know, you always have to sort of stand back and think, right, if they weren't in the trial, would I do this at this point? And do you know, if the answer's no, then it's like, right, well, we'll come back at some other time."*
>
> (ID 12, Physiotherapist, VEM)

One doctor had a more frank opinion to offer:

> *"…to be honest, we all, as consultants we break all the rules anyway."*
>
> (ID 22, Doctor)

Nurses were more likely to support an increased frequency of mobilisations for patients if each mobilisation had a functional or meaningful purpose. This concept is illustrated by a nurse involved in AVERT phase III who referred to some mobilisations as a 'tick' box exercise to fulfil a protocol. This may indicate that the rationale behind VEM is not explicit to some staff.

> *"…then you were going to them (number) times a day over and above what was standard care to say 'right, well come on, we'll just stand you up. Why? Well, I just want to give you a wee stand up and a walk to the toilet.'"*
>
> (ID 18, Nurse, VEM)

5.3.11 Organisation norms to change

A number of changes had occurred in stroke care. The organisation of stroke care was regarded as the most valuable change with the establishment of stroke units and provision of a quicker and more streamline service. Other important changes included the introduction of new medical interventions such as thrombolysis, new protocols for stroke referral and end of life care, improved patient education and a move towards early rehabilitation. Competing priorities would often determine the organisation's decision to implement a new intervention. The implications for service and staff outside of stroke care were also raised when discussing changes in stroke care.

> *" Erm, took a long time, but it did (adherence to stroke protocol) eventually come along, medical receiving took it on, but it, it can be hard work sometimes for medical receiving and I, I can see their point of view because they've got loads of different things coming in and things."*
>
> (ID 30, Nurse, non-VEM)

The approaches that staff described to introduce change differed. A risk-adverse approach to implementation was displayed by some hospitals, preferring to observe other hospitals' experiences of implementation first. A gradual and unplanned approach was adopted:

> *"…creeping services where they just, kind of, started doing it, and then it's got gradually bigger."*
>
> (ID 22, Doctor)

Other hospitals opted for a more systematic and protocol driven approach. The later often involved rolling out the change from an established centre to a non-participating site. Advantages of this approach included being able to tailor existing protocols to local needs, to diffuse enthusiasm amongst staff and to impart operational knowledge to those that were soon to be undertaking the change. Communicating the details of the change to the staff involved was integral in the planning stage of change. It was frequently mentioned that if staff felt included in the decision to implement and plan for the change they were more likely to come onboard and support it.

"I think the communication aspect of it I think having experienced change elsewhere before as well is like if you don't have everybody on board with the change, and people don't understand why the changes are happening, or what, what the changes are going to, erm, what value the changes are going to have, erm, that doesn't work."

(ID 30, Occupational Therapist, non-VEM)

There was acceptance that change took time and needed to be managed in parallel with the dynamic nature of healthcare systems making the process even more convoluted.

"…it was kind of shelved for a period of time and whatever, but then obviously other things have happened since then as well like, you know, kind of more even like government wise there's other things happen in the wider picture, which I think has obviously impacted as well on that and can take it further, but I don't know where it's at"

(ID 30, Occupational Therapist, non-VEM)

In some cases the emergence of research evidence had an immediate impact on stroke care. Two physiotherapists recall the day when the results from the 'Clots in legs or stockings after stroke study' where published.

ID 27: …"erm, clots was published we were all just, there was a buzz in the ward, erm, it was quite a..."

ID 28: It was literally...

ID 27: strange thing...

ID 28: it was literally the day, wasn't it?

ID 27: stockings off… [laughing]

ID 28: Erm, it started with one consultant saying… and then we had to wait the next day for the other consultant to come in.... and he was like no, I'm happy as well."

Paired interview ID 3 (ID 27- Physiotherapist, VEM; ID 28 - Physiotherapist, VEM)

The preference that physiotherapists stated for not using anti-thrombotic stockings was fitting with patient's low compliance to wearing the stockings. It may be that the implementation of an intervention depends on the level of congruence between the opinion of the individual HCP and the preference of the patient. It should be noted that this extract is an example of discontinuing an

intervention as opposed to implementing a new intervention or changing the way in which an intervention is delivered. This issue of patient preference has bearing for the implementation of VEM. Staff explained that there were times when patients preferred to remain sedentary as opposed to engaging in therapy or go for a walk. The most common reasons for this is that they were too tired, had a busy day of investigations or it was late in the day and would prefer to be seen in the morning.

> *"I'm sure most patients would, um, you know, the majority of patients would like more therapy and would benefit from it, but there'll be some that don't want any therapy. [Laughs].That's a different story."*
>
> (ID 13, Nurse, VEM)

The methods that were discussed to monitor the implementation of certain policies included audit, internal process meetings (quality circles), champions, hospital governance groups and regional forums. Some nurses and therapists did not view themselves actively involved in audit regarding this as the responsibility of the organisation. Process meetings were less commonly used than champions with both approaches used by one site during involvement with AVERT phase III.

> I: "*In terms of Very Early Mobilisation do you think either of these approaches [use of a champion and quality circles] would be required and if so work*?
>
> R: *because of the AVERT study both approaches have been used you know particularly discussions about how to make it better but certainly that requires someone to take a hold of it and they did."*
>
> (ID 9, Doctor)

Forum meetings were used more as a platform for information and exchange to enable staff to compare and reflect on the practices of other units. Staff defined a champion as an individual who had a genuine interest in the change and was naturally enthusiastic in driving it forward and had responsibility for cascading new information. The profession of the champion was less important with more emphasis on the individual's qualities and level of interest as this extract reveals when discussing a VEM champion. This contrasts to the theory that change is usually owned and operated by the discipline most associated with the new intervention as presented i.e. doctors with acute medical interventions

"I don't know. I think it could be a physiotherapist, it could be a medic, it could be a nurse. If it's someone who's enthusiastic and, you know, and quite charismatic really, that's what makes a difference just to put the point across."

(ID 10, Doctor)

The champion was seen to have a role in solving problems and maintaining enthusiasm in order to sustain the change. Having one dedicated person overseeing and co-ordinating the process may become onerous or result in the rest of the team developing evasive attitudes towards the change.

"If somebody (a patient) came in, right (name of staff) will get them tomorrow. Tomorrow's not good enough, we want them in today. So I think sometimes with champions, it can work in some instances, but in others you're making it a very one person dependent system, and if that person's not there, nobody else steps up in their place."

(ID 18, Nurse, VEM)

Therefore, success of the champion approach is reliant on having the organisation onboard and staff having a sense of responsibility.

"…says well it's their responsibility, but it's everybody's responsibility, so that's the, you know, the only negative thing."

(ID 30, Occupational Therapist, non-VEM)

The champion role was not solely viewed as an adjunct to one staff member's role but may emerge by staff collectively sharing experiences. Members of one stroke team visited another unit abroad, renowned for embedding VEM routinely in care, and on return to their own unit felt enthused and empowered to imparted new knowledge and principles of what they had experience elsewhere. This was believed to be the driver towards adopting early mobilisation in their practice. The following list of implementation strategies based on the current literature was presented to the HCPs to enquire about the specific use in the implementation of VEM; educational materials, small group education, audit and feedback, support tools i.e. decision making trees, reminders, financial incentives, revision of professional roles, local opinion leaders. There was no clear consensus regarding the most appropriate for use in the implementation of VEM. Education and revision of professional roles were met with most enthusiasm. Reservations were attached to feedback unless it was delivered in

an unthreatening manner and financial incentivises were believed to be unnecessary and unrealistic.

Provider characteristics

The themes within this category describe who is involved in mobilising the patient for the first time after stroke and providing subsequent mobilisation practice. The themes that are covered are as follows:

- Defining the providers
- Decision making
- Confidence and experience in stroke care
- Perceived risks and benefits
- Training and knowledge requirements
- Individuals' attitudes to change

The factors that influence the provider's decision making are identified. The provider's perceived benefits of VEM and the value of these benefits to patients are outlined. The levels of enthusiasm for VEM were assessed including the steps that individual staff members take to appraise the impact a new set of practices has on their role.

5.3.12 Defining the providers

The professional groups that were involved in the mobilisation of patients were physiotherapists, occupational therapists and nurses with a sizeable contribution from nursing assistants. Doctors, although not routinely involved in providing mobilisation, still viewed themselves as having a role in decision making.

> *"You'd need some weekend provision. And that might not just be the AHP [Allied Health Professional] side, it might also be medical staff saying oh that's okay occasionally."*
>
> (ID 11, Doctor)

"...[patients] deemed medically stable by us then we would encourage people to get up."

(ID 9, Doctor)

Physiotherapists when going to assess new patients frequently found that the patient had already been mobilised either by a nurse or independently.

"Even, even during the week it's often...because they (the nurses) might wash them and then just get them up in the chair. It's not always us (the physiotherapists) that's going to initiate it, do you know what I mean, um, particularly for the...you know, most patients, a lot of them are up out of bed before I've gone into them."

(ID 12, Physiotherapist, VEM)

There was a divide in opinion between physiotherapists regarding the role of nurses in getting patients up for the first time. One opinion, coming mostly from those working at AVERT phase III sites, being that "nurses are more than qualified to be able to make a clinical judgement about somebody" (ID 012, Physiotherapist) with the opposing view detailed in the following extract:

"I do take onboard they see the patients a lot more and they are able to decide whether they are struggling to help them with that transfer or not but for the initial assessment I do sometimes think that they have made a judgement and its not quite right."

(ID 6, Physiotherapist, non-VEM)

This issue of professional boundaries was a recurring theme throughout discussions. Some participants believed if these boundaries were relaxed and the sharing of traditional roles more customary this had the potential to increase the amount of mobilisation practice being delivered to patients.

*"…already we are seeing the blurring and I think given more of a blurring of the roles, you know…so if there was a quiet moment why you know two nurses could do …say walking a patient up the ward….why has it always got to be [*a therapist*]…if I take a gentleman that's in at the moment…I am just thinking why couldn't say an auxiliary nurse that free…that 5 minute walk done 3 times a day not necessarily by the physio might be the difference in getting that man home."*

(ID 2, Stroke Specialist Nurse)

5.3.13 Decision making

Prior to mobilising a patient for the first time all the respondents stated that the patient would have to be "medically stable". Staff defined medical stability as blood pressure, heart rate and oxygen saturation levels being within the normal ranges. A need for cardiovascular stability has been regarded by HCPs in other studies as a key consideration when mobilising patients for the first time.[178] [179]

> *"… and I think, um, general not wellness has always been a factor as well, so, um, physiologically, we're told always that if saturations are low or if they're tachycardic, or blood pressure's too high or low, then they don't get mobilised."*
>
> (ID 22, Doctor)

Other terms such as "medically unfit" and "medically unwell" were also used. It is unclear if these terms were used in addition to "medically stable" and had different meanings or used interchangeably. Other factors such as level of consciousness, headaches and temperature were also included in the definition of "medically unfit". It may be that "medically stable" relates to cardiovascular stability while "medically fit" relates to the patient's general health status.

> *"Other reasons for not getting people up? Pain, not that common with strokes I suppose, headaches and things you get with it. Headaches and drowsiness but, I suppose, that's a medically unfit patient with a headache or drowsiness. They probably need to just take things more slowly."*
>
> (ID 10, Doctor)

Signs of medical instability were monitored during the first mobilisation using either physiological monitoring equipment or subjective assessment. The need for medical stability appeared to be a communally approved criterion evolved from clinical opinions; "we're told always" rather than evidence-based. This prerequisite for medical stability was only challenged by doctors.

> *" Well, I don't, I don't, um, it's not that I don't believe it, nobody can give me any evidence [voices overlap] to say that it's a harmful thing to-to mobilise somebody with those issues. Um, and I suppose at the moment, nobody can give me a lot of evidence that only mobilisation…definitely, definitely, definitely is the right thing to do either."*
>
> (ID 22, Doctor)

Doctors viewed the patient's ability to achieve sitting balance as an important factor in the decision making process in mobilisation a patient for the first time. This agrees with the existing theory that concerns are related to the area of non-expertise i.e. doctors towards the physical aspect of mobilisation.[178]

> *"I guess the key thing would be that the physio would decide if the patient had enough sitting balance to get up to a chair would be the first step and if they didn't they couldn't and if they did you know they would be got up".*
>
> (ID 9, Doctor)

In contrast when posed to nurses and therapists in later interviews sitting balance was not considered as a determinant to mobilising patients.

> I: "*Sure, if they've got enough sitting balance?*
>
> R*: Well, he hasn't got any, but he's safe enough in...we've got an appropriate chair for him."*
>
> (ID 30, Nurse, non-VEM)

Unlike therapists, the level of weakness the patient had seemed to be more of a deciding factor in whether a nurse would mobilise the patient for the first time. This depended on "*what nurse was on [*shift*]*" with some nurses going ahead and mobilising patients regardless the degree of weakness: "*especially if they look like they have got a dense weakness there, we would normally just hoist them anyway regardless*". Nurses believed they take the lead from physiotherapists with regards to mobilisation, especially of patients with more complex needs, but it could be that nurses underestimated the extent of their role in the mobilisation of patients. One strength of the focus group data is that the participants can choose whether to agree or disagree with the other participants' impressions or opinions. In the conversation below, the nurse explains that she usually relies on physiotherapists however the physiotherapist present in the same focus group quickly interjects the nurse to correct her colleagues perceived role in mobilisation.

> *ID 014: "It's taking the lead really from you.*
>
> *ID 012: Well, it's not always the case, because yous are often...*

ID 014: Aye, no, at the weekend, at the weekend, uh huh.

ID 012: You'll always get people up.

ID 014: Aye, we still do. Unless they're going to be a huge mobility risk and then we would say, do you know, it's not really advisable for us, we need to wait for physios or other therapists to come in and assess them."

Focus group 3 (012 – Physiotherapist, VEM; 014 – Nurse, VEM)

Other factors including the patient's risk of complications, level of consciousness or fatigue played a role in influencing the HCP's decision to mobilise a patient for the first time.

"I mean, he was medically kind of stable enough, though, to kind of get him up, but he had gurgle chest, so getting him up to sit in the chair is much better than, than being in the bed anyway"

(ID 30, Nurse, non-VEM)

Low levels of consciousness did not discourage the mobilisation of a patient; therapists reiterated the need for a "dynamic risk assessment" to detect any changes in the patient's medical status in response to being upright. The following extract from a physiotherapist provides a step-by-step commentary of the typical decision making process when mobilising a patient for the first time.

"…then actually if they are medically stable regardless of their GCS [Glasgow Coma Scale] we would probably get them up but not necessarily out of bed but we would assess them sitting over the edge of the bed to see what their arousal state is like and see if they are actually waking up to any stimulation and then from there check monitor their cardiac, blood pressure stability and if we feel that it is appropriate we will get them out of bed with the appropriate means…but of you feel it is still a wee bit too early then we would get them back to bed and go back the next day…GCS 3…mmmm…maybe just put them back to bed depending if there are 98 [years of age] or whatever but yeah if they're starting to come round we would probably push them."

(ID 4, Physiotherapist, VEM)

There was some agreement between nurses and physiotherapists that nurses were more tentative than physiotherapists when deciding to mobilise a patient for the first time. Furthermore, some nurses were critical of nursing colleagues for their overly zealous approach to mobilisation while it was physiotherapists that considered themselves to be the pro-active group in having a more

"aggressive" approach to mobilising patients than nurses. This was not always the case with one nurse posing the following question;

> *"And sometimes we take a risk even when they are not medically stable don't we?"*
>
> (ID 3, Nurse, VEM)

The majority of nurses and therapists regarded fatigue as a direct consequence of stroke which may have resulted in a more cautious or protective approach to mobilising patients had it been related to some other cause such as disturbed sleep patterns or associations with a result of low mood.

> *"I'm a bit of a stickler for people sitting out [of bed] and I, I sometimes get this chat about they've not been sat out cos they were too sleepy. But I mean it's all relative, and yeah, some people occasionally are too drowsy…even to sit out, and certainly people can be too drowsy to have physiotherapy, but, yeah, I'd just…occasionally I've thought perhaps just needed to be slightly more…"*
>
> (ID 11, Doctor)

Relatives/carers placed value in knowing their relative had been up sitting in a chair, often asking if "*they been up to sit today*?" when they phoned in the morning. The meaning of mobilisation to relatives did require special consideration. Although not usually reported as a reason for not getting someone up early after stroke, mobilisation may provide relatives/carers with false hope which was particularly relevant for patients with poor rehabilitation potential or prognosis where patients may appear to look a lot better when sitting upright.

> *"…maybe they are not for resus but they are still for active treatment then to sit someone out that may give their relatives the wrong impression so we have to take that into consideration as well so again kind of weighing up the individual and thinking well is it appropriate that they sit out"*
>
> (ID 3, Nurse, VEM)

5.3.14 Confidence and experience in stroke care

The confidence and experience of staff working with acute stroke patients was considered to be an influencing factor in initiating and providing mobilisation to patients. It would often take a more confident nurse to make the decision to

mobilise patients for the first time. It was unclear if these confidence issues were related to a lack of skills to assess how patients' impairments may affect mobilisation, experience in transferring stroke patients or knowledge of the most appropriate method of transfer or seating. At one hospital, two physiotherapists agreed that NIHSS training for nurses was linked with improved confidence. This subsequently led to a more pro-active approach to mobilising patients for the first time.

> *ID 27: "…maybe it's [NIHSS training], you know, giving them a bit of confidence that they're actually having to look at somebody's, you know, leg strength and then think…".*
>
> *ID 28: And sensation, and...*
>
> *ID 28: ... you know, actually maybe you can get them up."*
>
> (Paired Interview 3, ID 27 – Physiotherapist, VEM; ID 28 – Physiotherapist, VEM)

In cases of uncertainty nurses preferred to wait for the physiotherapist to seek advice on mobilising the patient for the first time.

> *"Sometimes if you are not sure how to transfer them (the patient) you would wait until we (the physiotherapists) came...Or you weren't sure what chair you wanted them in or whatever then they would wait until we came in normally then."*
>
> (ID 19, Physiotherapist, VEM)

The focus groups gave participants the opportunity to compare their approach, at a professional level, to mobilising patients for the first time. In one group two nurses explaining their approach as individual, based on clinical judgement and has its limits i.e. not mobilising a patient considered to be medically stable. The physiotherapist in this same focus group uses this as an opportunity to express her opinion that physiotherapists take more of a risk with these types of patients than nurses, which was agreed by the nurses.

> *ID 21: "And you know the ones that you can try.*
>
> *ID 20: You know the one you can get.*
>
> *ID 21: Try, you know the ones you just can't.*
>
> *I: Okay so what you are saying there about fit, I guess you are saying*

medically fit…?

ID 21: Was she medically fit aye.

ID 20: Medically if there is somebody then really in the red, we put off till the next day…

ID 19: I think sometimes we maybe risk take more than you do.

ID 21: Aye definitely, definitely."

Focus group 5 (ID 19 – Physiotherapist; VEM, ID 20 – Nurse, VEM; ID 21 - Nurse, VEM)

Being familiar with how others work and being able to draw on each other experiences was regarded with much importance. Therapists who worked together with patients referred to this joint working as intuitive with "non-verbal communication" making mobilising patients more natural and efficient. This intuitive working is also represented by the way in which therapists often interacted with each another during discussions, particularly during the paired interviews. The following extract from a conversation during a paired interview between two physiotherapists about the rehabilitation environment. It provides a snapshot of how the two physiotherapists were at ease with one another, talking over one another and at times finishing off each other's sentences. This indicates the close bond that has developed between two colleagues working together.

ID 027: "…rehab's a much better environment for them because they feel they're actually…

ID 028: …getting more therapy and getting somewhere rather than…

ID 027:..at rehab to accommodate, erm, trips out and things even that, which…

R 028 :…they've got no chance of getting in the acute stroke unit.

R 027:…Even getting outside into the…

R 028:…they've got nice grounds and they can get, it's on the ground floor so they can get taken outside…"

(Paired Interview 3, ID 27 – Physiotherapist, VEM; ID 28 – Physiotherapist, VEM)

As well as length of time working in stroke care it was important that staff also

had recent work experience in stroke rehabilitation to account for the changes that had occurred in recent years.

> *"You see I think that it's quite old school – to think that someone has a chest infection, spiking a temperature, on oxygen you are probably more likely to want to keep them in bed than wanting to get them out of bed…"*
>
> (ID 4, Physiotherapist, VEM)

5.3.15 Perceived risks and benefits

Therapists and nurses associated mobilising patients within 24 hours and at a higher intensity with the risk of doing "*too much too soon*" (ID 019, Physiotherapist) and an increase in patient falls as opposed to more direct medical risks. The majority of staff that mentioned medical risks such as changes in blood pressure were nurses and doctors.

> *"…probably most blood pressure flux [fluctuation] would be the thing that would intuitively concern us if people lost their blood pressure responses and if they stand up and their blood pressure falls then it may extend any deficit and that sort of thing."*
>
> (ID 9, Doctor)

A few nurses believed that if a patient was going to deteriorate, this would happen regardless of them receiving VEM or not. Increased fatigue, "*if that counts as risk*" (ID 010, Doctor), was linked with an increase in mobilisation of patients. Staff at one hospital had been involved in a study investigating the effects of augmented therapy recalled the recurring fatigue patients allocated to the intervention group experienced.

> *"…and that was just physio, but they were also timetabled to have OT and if appropriate still having speech therapy. So some of them were actually physically tired."*
>
> (ID 26, Physiotherapist, non-VEM)

Therapists aimed for a balance between rest and activity for patients which may partly explain this concept of "*too much too soon*". Rest was seen to have an important role in patient rehabilitation. Increasing the intensity of mobilisation may influence this balance and result in patient exhaustion or "knock the patient back". Staff did not specify an optimal length of time for mobilisations

such as the sitting in a chair seeing it more dependent on the preference of the individual patient. It was acknowledged that the impact of remaining in one posture for prolonged periods of time may begin to counter any positive effects that being upright may have as the scenario in the following extract explains.

> *"I know he wants to be sitting but actually it's working against him just now because, because he was so busy fixing everything, when you tried to stand him up he couldn't, he just kept, he was half bent over and whatever so it was around sort of saying to the girls I know he is saying that he wants to be sitting up all the time but actually he needs to go and lie down for a wee while because he needs to get stretched out."*
>
> (ID 19, Physiotherapist, VEM)

On the other hand, risks associated with bed rest were more readily identified by staff and included higher risk of medical complications, a poorer recovery, increased length of acute stay and reducing the patient's rehabilitation potential.

> *"I think that any rehab potential would be just significantly decreased – its just means that they would have progressed in the way that they would have done and if they had not had that earlier input".*
>
> (ID 1, Physiotherapist, VEM)

Again doctors were the only professional group to question this way of thinking believing that it lacked hard evidence.

> *"Yeah I guess there would be…in the longer term there would be a risk of less mobility and…ehm…contractures and things went on that long but you would suspect that there would be an increased risk of chest infections or DVTs if people well less mobilised yet that is not convincingly proven."*
>
> (ID 9, Doctor)

One team shared their experience of a patient who had a stroke whilst on holiday abroad and had not been mobilised during his acute hospital stay. When the patient was transferred back to Scotland stroke unit staff were horrified that bed rest was still in practice:

> *"And he found that really stressful, he wanted to get up and do something. So I just thought that was really interesting, we can't believe somebody being kept in bed for two whole weeks post-stroke."*

(ID 12, Physiotherapist, VEM)

Patient safety was high on the agenda for staff when discussing the mobilisation of acute stroke patients in particular those patients with perceptual or cognitive issues or were agitated. An increase in the number of staff injuries were also connected with increased patient mobilisation if it was not performed correctly.

ID 3: "*…there are the ones that are so unsafe to be…you they would be better out of bed but maybe its just not possible…and they try to get up and walk.*

ID 4:*…because of their perceptual difficulties…we would still get them up, get them out and moving…but it may be getting them up to sit and back to bed because they are safer in bed than in a chair."*

Focus group 1 (ID3 – Nurse, VEM; ID4 – Physiotherapist, VEM)

Two previous studies have revealed conflicting evidence regarding opinions of early mobilisation and stroke type. One study revealed that HCPs had more concern over mobilising patients with a haemorrhage than patients with ischemic stroke,[179] while the other showed that HCP opinion to mobilise early was not influenced by stroke type.[178] The immediate reaction of staff in this study was that their opinion of the VEM would remain the same regardless of stroke type. Nurses and therapists stated that stroke type was often not known at the time they currently mobilise the patient anyway. On further probing staff did go on to state a "little" concern for mobilising haemorrhagic strokes within 24 hours with a potential of further bleed. This didn't necessarily equate to staff excluding VEM but adopting a more cautious approach to mobilising these patients for the first time; haemorrhagic stroke patients were viewed to have a more variable clinical presentation than ischaemic strokes and likely to require extra monitoring.

R: *"I would say we are still a little more cautious with haemorrhages but um we obviously monitor everybody um, keep an eye but I do think um we are more, more aware.*

I: *And why do you think that is?*

R: *I don't know just in case there is a further um, a further haemorrhage, in case anything…gets worse."*

(ID 23, Physiotherapist, non-VEM)

There was strong agreement that if VEM were shown to be effective for a subgroup of patients this would compromise the care of other patients not receiving VEM. The following two extracts shows that this consensus was evident within focus groups (FG5, first extract) and across focus groups (FG 4, second extract) and interviews (PI1, third extract).

ID 19: "I think it's hard to, you know, what we've said and what I've sort of reported back er to my managers and whatever is that if we, you know, if we use AVERT as a, as an example, if we have a patient in the interventions group on AVERT then the other patients suffer as a result of that, you know, especially if they are in the higher level groups, you know, because tell all you to deliver what you need to deliver for the trial then somebody else…

ID 20: Is not going to get their session.

ID 19:…you know, gets their session shorter or they just don't get seen that day or whatever um, you know…"

Focus group 5 (ID 19 – Physiotherapist; VEM, ID 20 – Nurse, VEM; ID 21 - Nurse, VEM)

"So if you then feel that you're concentrating more on a certain patient or a certain group of patients, something else has got to give, because you're going to have to drop something else to do that. So at what cost is that going to be?"

(ID 17, Physiotherapist, non-VEM)

"I was very much how would people feel lying across from somebody that's getting loads of attention and like support and things whereas you got it once a day, do you know what I mean, you'd be a bit like mmm".

(ID 24, Nurse, non-VEM)

The flipside to this argument was that an evidence-base for VEM may actually strengthen the campaign to get patients onto the stroke pathway more quickly. The focus for staff was to deliver good stroke care whether the patient received VEM or not.

"Um, it's meant that in general terms, we're getting people imaged quicker than we would have otherwise, even if they've not, um, even if they're not getting thrombolysis, um, we're getting people to the stroke

units quicker than we did as well, so, so, it's, probably is a side benefit – all the patients that aren't getting thrombolysis or even, aren't even getting assessed with thrombolysis, are getting a better deal."

(ID 22, Doctor)

Staff highly valued early rehabilitation and believed that it provided benefits to patients. The same benefits, yet with additive effect, were seen for VEM.

"Ehmm…I guess the quicker they start the quicker they back on their feet which should translate to better functional outcome, shorter hospital stay and less risk of early complications would be the guess."

(ID 9, Doctor)

This additive effect of VEM may only be observed in subgroups of patient.

"…there are some patients that would very much benefit from it and there's others that, you know, might not make a huge difference in the overall outcome."

(ID 30, Occupational Therapist, non-VEM)

One of the most frequently mentioned benefits of VEM was the improvement of the patient's mood. Staff believed getting patients up provided them with the stimulation of the ward environment and a sense of 'normality'. It allowed them to engage in their surroundings and if they were sitting up or mobilising more frequently around the ward that would give them more opportunity to interact with other patients. The risks and benefits of VEM as identified by staff are summarised in Table 5-4.

Table 5-4 Perceived risks and benefits of VEM

Perceived benefits of VEM	Perceived risk of VEM	Perceived risks of bed-rest
• Improve patient mood • Improve patient confidence • Improve patient motivation • Increase interaction between patients	• Stroke extension • Fluctuation in blood pressure • Increase in patient falls • Increase in staff injury • Impact on service i.e. other patients • Unrealistic perceptions for patient • False impression of recovery for families	• Increase risk of immobility related complications; pressures sores, deep venous thrombosis, chest infections, subluxations, contractures, muscle wasting, reduced range of movement • Reduce mobility • Increase length of acute hospital stay • Reduce rehabilitation potential • Reduce long term recovery

Ranked in order of frequency i.e. improve patient mood was the most frequently reported benefit of VEM

5.3.16 Training and knowledge requirements

By and large, technical training of existing ward staff was not viewed as a prerequisite to implementing VEM. Providing training in, for example, moving and handling was given little regard with the issue of "*performance*", that is actually employing the skill in real-life, taking precedence. Educating staff in the theoretical principles of VEM was seen to offer more benefit by incentivising staff to adopt and sustain the intervention in clinical practice.

> *"The education, the skill sets there, that's more say performance…performance management. So I think it's more the education about why early mobilisation and what benefit it's going to be, rather than how to actually do it."*
>
> (ID 18, Nurse, VEM)
>
> *"The nursing staff on this ward are so good there stroke specific trained so they know how to mobilise patients."*
>
> (ID 8, Nurse, non-VEM)

At one hospital, the training of nursing staff to encourage them to be more involved in the mobilisation of patients especially at the weekend proved unsuccessful in changing behaviour. There was a sense that physiotherapists felt nurses did not see this as integral to their role while the nurses were more likely to reason this with a lack of time and competing ward priorities.

> *"And I mean they have access to the chairs, so if somebody has got denser and needs a more supportive armchair then they're in the dayroom and I have over the years spent numerous sessions showing people how to use them correctly. So they (the nurses) should know why they would use it and they have access to them."*
>
> (ID 25, Occupational Therapist, non-VEM)

Assessing mobility and the act of mobilising a patient was considered to be a complex task requiring specialised input as this physiotherapist explained:

> *"I think with that they would have to do a full neuro assessment because everything that you do with that neuro assessment helps then you decide how that patient is going to manage its not…I mean there are some mobility assessments that you don't need a trained therapist you know to carry out…however there are so many different aspects that can affect the way a patient is mobilising or transferring".*

(ID 6, Physiotherapist, non-VEM)

5.3.17 Individuals' attitudes to change

Nurses recognised that although change may appear a 'simple process' on paper there was fear; believing that if they got it wrong there are huge consequences for the patient. Nurses using thrombolysis as an example did reveal that when the change was put into practice fears were often alleviated and the practice became "normal".

"But it's like, it's like a new job. So once you've got the process up here, and you know what's going to happen as soon as that patient comes in, it's a process you get...it's like doing your job every day. There are a lot of things now that you used to have to think carefully about, now you don't...you just know that that's what you've to do next, so you get on wi' it."

(ID 13, Nurse, VEM)

Doctors were more confident when discussing change, most likely due to them being the professional group most likely to lead or be heavily involved in the implementation of an intervention, while nurses and therapists were more tentative towards change. A number of therapy staff felt that they were up-to -date with stroke guidelines but it was more an issue of resource that prevented implementation. Staff appeared to be aware of current policy and research and viewed the emergence of clinical guidelines and NHS performance standards such as Health Improvement, Efficiency, Access and Treatment targets as the main drivers of change. Policy often resulted in the re-design of stroke services, for example, the working time directive resulted in less medical cover being provided to off-site units which impacted on how care was organised and the role of staff. Staff showed signs of appraising their actions:

"We have been caught out a couple of times and we recognise that ourselves and its something that we are sort of actively trying to, to make better I think."

(ID 19, Physiotherapist, VEM)

Staff appreciated that an intervention implemented in real-life may not have the same effect as when it was under study in a trial. There was a sense of disappointment that the results didn't meet expectations.

"It [thrombolysis] doesn't appear as successful as the statistics would have you suggest."

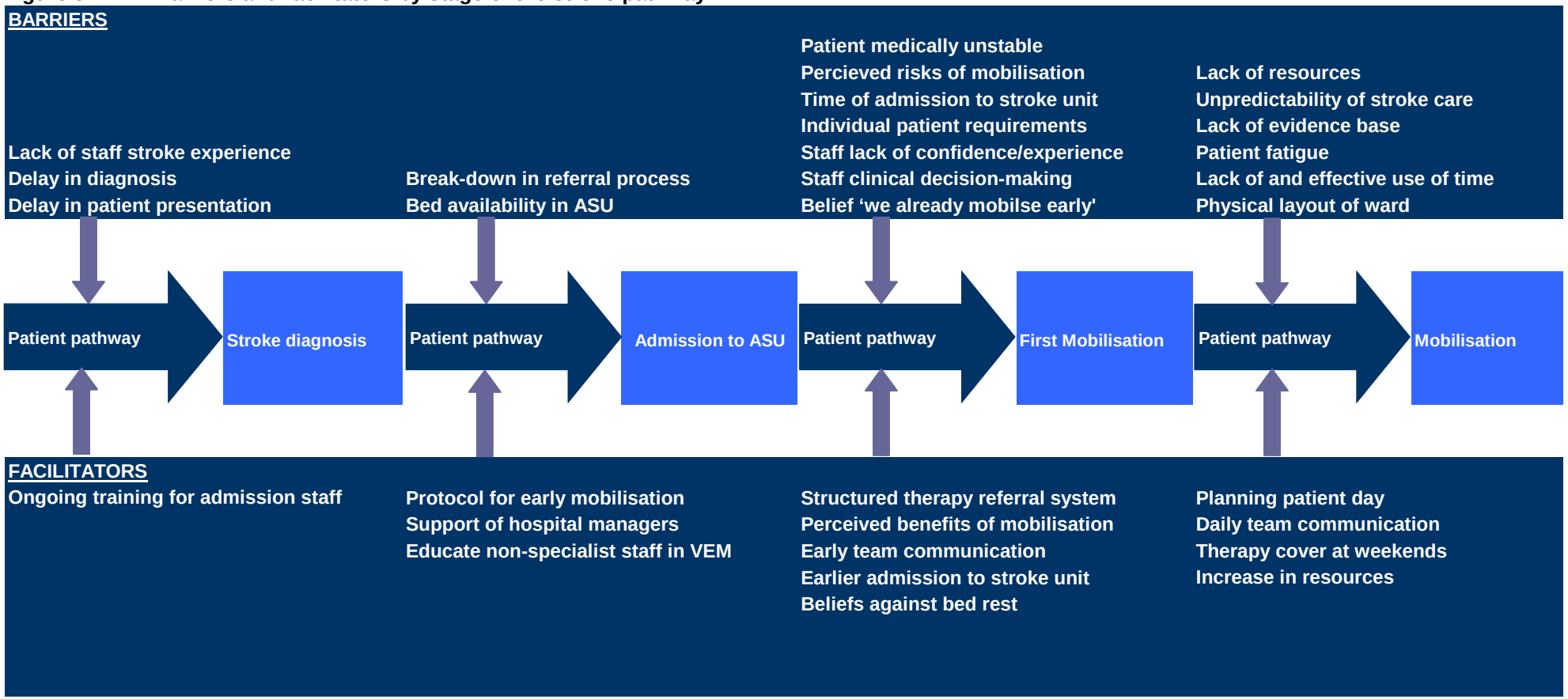
(ID 27, Physiotherapist, VEM)

5.3.18 Summary of barriers and facilitators

Barriers to mobilising patients within 24 hours included lack of staff stroke experience, delays in diagnosis and patient presentation to hospital, break-downs in the referral process, lack of bed availability in the ASU, patient "medically unstable", perceived risks of mobilisation, time of admission to stroke unit, individual patient requirements, staff lack of confidence/experience, staff clinical decision making and the belief by staff that 'we already mobilise early'. Barriers to increasing the frequency of mobilisation patient had been mobilised for the first time, included a lack of resources, unpredictability of stroke care, lack of evidence-base, patient fatigue, lack of and competing demands on time and the physical layout of ward.

Facilitators to mobilising patients within 24 hours included the provision of stroke specific training for hospital admission staff, a protocol for early mobilisation, support from hospital managers and the education of non-specialist staff working in general medical units in the principles of VEM. A structured therapy referral system, perceived benefits of mobilisation, early team communication, earlier admission to the stroke unit, planning the patient day, daily team communication, therapy cover at weekends and an increase in resources, were the facilitators identified to mobilising a patient more frequently within the ASU. These barriers and facilitators are summarised for each stage of the stroke pathway in Figure 5-1.

Figure 5-1 Barriers and facilitators by stage of the stroke pathway



5.4 Discussion

This study has provided rich narratives about HCPs' experiences of working within an ASU. Barriers and facilitators to implementing VEM have been identified and a set of beliefs that HCPs hold towards VEM has been formulated.

Summary of key findings: barriers and facilitators identified

As previously explained, information about barriers and facilitators is particularly salient for a complex intervention such as VEM. Factors that may promote or inhibit the embedding of VEM in routine practice were identified for each stage of the stroke pathway. Accessing the patient during the acute stage, with the patient being off ward for tests was viewed as problematic by staff. Interestingly, the observational data estimated that the time spent off the ward by patients was only 3.7% which illustrates that potentially, there is incongruence between perceived barriers and real-life (Appendix 14). The need for more staff was an automatic and recurring response when the participants were asked what would be required to facilitate VEM in routine clinical practice. Few participants were able to provide details of the form that this required additional resource may take and fewer (two participants at the same hospital) challenged that the focus should be more on how best to use current staffing resources.

At a site level, the same barriers and facilitators to VEM were raised regardless whether they had experience of the trial or not. Staff currently involved in AVERT phase III were more forthcoming in identifying requirements for the delivery of a rapid mobilisation service to patients such as an outreach service to wards outside the ASU. Making comparisons between sites is important to identify the factors that may predict implementation. For example, staff from all but one of the sites believed that communication between nurses and therapists was cohesive, fluid and responsive. At the other site, also a non-AVERT site, there were signs of tension between staff which impacted on the opportunity for mobility practice. Comparing sites is useful to identify the absence of key processes or components of care. This example highlights that communication is pivotal to patient mobilisation and that targeted strategies are

required to prepare such sites prior to implementation of VEM.

Barriers and facilitators are often classified into environmental or organisational, however this requires knowledge about the cause of the barriers and facilitators. For example, lack of resources may be an individual's perception of the organisation rather than the organisation not providing enough staff to organise the system. Bed availability may be due to the break-down in operating the system, not the actual system put in place by the organisation.

Summary of key findings: healthcare professionals' beliefs

The main beliefs about VEM were centred around the perceived impact on the patient's outcome and the HCPs routine practices. More specifically, it was believed that VEM:

- is already being conducted
- relies on the time of symptom onset being available
- is beneficial to patients but may have some risks
- is associated with an increased workload
- is a shared task between therapists and nurses
- requires tailoring to meet individual patient requirements
- is appropriate only for patients who are medically stable

Each of these beliefs will be discussed briefly in turn. All of the participants were aware of the current Scottish Intercollegiate Guideline Network which states that "stroke patients should be mobilised as early as possible after stroke".[2] Therefore, HCPs may have been eager to portray themselves as adhering to the current guideline about early mobilisation. This may explain their immediate response that they are already practising VEM when first asked. When the definition of VEM was reiterated and participants were asked to compare the VEM principles with their current practice and processes, it emerged that staff were actually mobilising patients for the first time as early

after stroke as they believed was possible. Indeed, the observational data (Chapter 3) did indicate that the time of first mobilisation was either more than 24 hours or unknown, conflicting with HCPs beliefs of what happens (Appendix 15). Integrating the qualitative and quantitative data in this way (triangulation) raises an interesting question about how behaviour can be perceived to be different to that which actually occurs. The more general question that is raised here is - how best to define VEM so that it is distinguishable from current practice? This is a common issue associated with complex interventions. Current mobilisation practice appeared to be highly variable (patient and context dependent), implicit ('just something that we do') and largely undefined as a specific intervention in acute stroke care. As the time from symptom onset to hospital arrival is the factor determining eligibility for many acute stroke interventions this does pose challenges in being able to ascertain this information and subsequently deliver the intervention within an acute timeframe.[193] The belief that VEM is beneficial was based on the understanding that bed-rest can result in immobility-related complications.

The association of VEM with an increase in workload was a prevalent topic discussed amongst all therapists and nurses, particularly therapists. Interestingly, for HCPs working at non-AVERT sites and with no experience of VEM this perception had been shaped through conversations with other local HCPs who were working at AVERT phase III sites and delivering the intervention. Some HCPs did believe that perceptions of increased workload could be alleviated once experience of delivering the intervention was gained. This raises once again the issue of contamination of complex interventions, initially presented in Chapter 1. The AVERT phase III intervention protocol prohibits communication between trial and non-trial staff. Contamination in the form of current behaviour inadvertently being changed due to attempts to adopt the intervention under study, does not appear to be the issue here. More disconcerting are the negative preconceptions around VEM as a result of communication between trial and non-trial staff.

Staff regularly stated that their current workload was busy enough. Although, there was a sense (when comparing findings in Chapter 3) that staff tended to over-estimate and make assumptions about the length of time a patient was

inaccessible during the day. Perceptions about the patient's accessibility and readiness for therapy/mobilisation resulting in missed opportunities. It may be that staff need to realise that they may not be using time as efficiently as they believe. The Productive Ward: Releasing time to care™ programme by the NHS Institute for Innovation and Improvement provides an example of how this realisation could be provoked in real-life. This initiative aims "to empower ward teams to identify areas for improvement by giving staff the information, skills and time they need to improve the way they work and the care they provide".[194] Staff are video-recorded during routine practice (referred to as an 'activity follow') and then these recordings are fed back directly to the staff included. Exposing staff to their own actual data separated their beliefs about goings on and reasons for things occurring with reality. The video recordings from these 'activity follows' provided a sense of revived individual responsibility amongst HCPs and reactive engagement to collectively identify problem areas and provide simple solutions.

The majority of participants viewed the first mobilisation as a shared task whilst in a previous study the majority of nurses and therapists believed that each professional group had independent responsibility.[178] Staff worked together to deliver mobilisation to patients and were cognisant that the success of this depended not only on their individual skill-set but also understanding and having confidence in the skills of their colleagues. At the sites where this was not the case (evidence at two sites) there was an obvious and historical divide between the nurses and therapists where roles appeared to be based on traditional models. There were occasions where the physiotherapists believed that the nurses had made the incorrect judgement. At one AVERT phase III site the physiotherapists were unclear as to who actually delivered the first mobilisation for intervention trial patients. This illustrates that there is some evidence that the division of labour may not always be explicit and this can differ markedly between sites depending on the skills and experience of staff.

There were a number of patient level factors that contributed to the decision whether to mobilise a patient for the first time. Many patients have comorbidities which may determine the level of physical activity that they are able to engage in. The factors were not only multiple, varied by individual

patient but were also considered simultaneously making it challenging to identify the key factor(s) driving decision making. For example, HCPs commonly used trade-offs when deciding to mobilise a patient up-to-sit in a chair for the first time:

- increasing fatigue levels versus creating a more stimulating environment
- reduced consciousness level versus reducing risk of chest complication

This decision making was an intuitive process for most staff when mobilising a patient for the first time and it was believed that the same principles would apply to VEM. Reliance on subjective evaluations of patient progress based on intuition or clinical experience is recognised elsewhere.[195] Medical stability was the most pressing issue for professionals, which is in line with a previous study whereby along with the level of consciousness, medical stability was considered one of the most important factor in deciding whether or not to mobilise a patient.[178] There is a need for the term "medical stability" to be clearly defined and for more evidence around the mobilisation of patients considered to be "medically unstable". The patient's level of consciousness was a key factor in deciding whether or not to mobilise a patient both for the first time and when continuing mobilisation practice. Defining consciousness was difficult due to the number of terms used and an acceptable level of consciousness was not agreed; it was clear that if patients were almost asleep staff questioned the worth of getting them sitting up in a chair.

Strengths and limitations

The findings are based on a relevant sample of HCPs and provides multiple and diverse perspectives. One limitation in the study was that no nursing assistants participated. Nursing assistants are considered to be the group who deliver a large proportion of patient care and are involved in the day-to-day mobilisation of patients.

The findings from triangulation of data (using the observational data and the qualitative data) presented at points through this discussion have proved useful in highlighting discrepancies between what staff believe they do and what they

actually do. This emphasises the importance of sharing the findings of clinical effectiveness activities with staff. Having being involved in AVERT phase III in the capacity of Trial Manager it could be argued that participants may have been less reluctant to highlight any problems or provide critical responses, portraying an overly-optimistic picture of implementing the trial intervention. The frank nature of the data presented in this Chapter does provide some support against this argument. Developing relationships with participants during the conduct of qualitative research is an essential part of the process and it is believed that having a pre-existing relationship with the majority of participants enhanced discussions and facilitated open and honest answers about topics that they understood the interviewer to have an appreciation for.

As previously noted, one of the shortcomings identified by Lewin et al (2009) was that qualitative findings are not often integrated with the outcome data of the evaluation.[171] The findings of this process evaluation could be integrated with the outcome data from AVERT phase III. Process data could be used to explain any variability in the effect size of VEM. For example, staff frequently highlighted that rehabilitation had to be tailored to meet the needs of individual patients. This may result in staff being unable to deliver VEM in a standardised way and explain variation in outcome.

Chapter 3 revealed significant differences in the level of upright activity between the sites. Adjusting the analysis for baseline level of severity and level of mobility did not explain much of this variation. Therefore, it could be speculated that other factors such as differences in current practices and ward-layout (as informed by data from researcher observation and interviews) may explain this. The hospital that had the highest level of upright activity also had more open-planned bed bays, more formal MDT meetings per week and a higher presence of therapists on the ward throughout the day.

Prevalence data to gauge the importance of each of the barriers and facilitators were not provided. Alternatively it could have been counted in relation to the number of participants who raised it across the entire data set. However, this could be potentially misleading as a barrier that had a high prevalence could have been the result of just one person repeatedly saying this.

This study is limited in providing details on the relative importance of barriers and prioritising of the barriers. This may have particular relevance in the area of implementation science whereby the relative importance of each of the barriers and facilitators may be required to guide investment decisions around implementation strategies. The use of discrete choice experiments (DCEs) to investigate preferences may be of value in implementation science. Discrete choice experiments present people with a range of choices requiring them to state a preference for a given scenario. Each choice consists of one or more hypothetical options and for each choice people are asked which one they would choose. It works on the assumption that decisions are based on multi-criteria and not just one factor (attributes). Forcing people to make choices and trade-offs (between barriers and facilitators) could ensure that implementation strategies are tailored to the specific preferences and trade-offs of those who will actually be delivering the intervention. The barriers and facilitators identified here could be used to inform the basis of a DCE. The analysis of relative importance of each of the attributes may reveal that the decision to mobilise is strongly influenced by the need for the patient to be medically stable. Thus, indicating that the greatest effort in developing implementation strategies should be invested into defining the term 'medically unstable' and, as required, alleviating HCPs' concerns of mobilising patients confirmed or perceived to be medically unstable.

It has been recommended that implementation science could be significantly improved by taking a more systematic approach in using theory to study healthcare implementation. The main limitation of this qualitative analysis is the lack of use of a theoretical framework. This is important to increase the accessibility and usability of the knowledge that has been generated. The use of an implementation or behavioural change theory may have assisted in identifying the determinants of change and if those determinants are modifiable. One sociological model called the Normalisation Process Model is specifically designed to study complex interventions and enquire what people do to make a complex intervention workable in real clinical practice.[196] The model proposes that the success of a complex intervention should be interpreted in relation to the workability and integration of it in practice. This model has since been

developed and reoffered as the Normalisation Process Theory (NPT). In 2005, the UK House of Commons Health Committee emphasised the need for an improved understanding of the implementation process and NPT may offer the conceptual tools to satisfy this requirement.[31] Further models and theories of implementation and behavioural change are described in Section 7.5.2.

A flexible seven day working week would mark a significant turning point for therapists and certainly, although not met with much enthusiasm here, signs of this are already evident in some parts of the UK. The Chartered Society for Physiotherapy guidance has already made stipulations for such services in that they should be adequately funded and piloted prior to implementation. The cost-effectiveness of such a service in stroke care needs to be determined. One of the ten points for action outlined in the national stroke strategy is for intensive rehabilitation "operating across the seven day week".[17]

As noted in Chapter 1, the uptake of a complex intervention depends on the responsiveness of those receiving it. Very early mobilisation requires patient participation and possible self-practicing which has implications for compliance. This study did not interview patients to gauge their perceptions of the intervention. Staff often raised patient preference as a factor to consider before and during mobilisation as was the response of relatives. A previous study reported that the majority of nurses (71.8%) and physiotherapists (57.1%) were prepared to mobilise a patient whatever the families/patients view.[178] Staff were observed on the wards (Chapter 3) using motivational and negotiation techniques with patients initially unenthusiastic to mobilise. Staff believed that the patient's response to VEM would be varied; with some patients in favour of undertaking more mobilisation while others were not. This concept could be explored by conducting interviews with either stroke survivors or patients that have taken part in AVERT phase III. If trial patients are to be interviewed it may only be feasible to do this on completion of their involvement in the trial. However, recall may pose a challenge. If the blinding to group allocation of the interviewer and patients could be guaranteed and that interviewing patients would not pose any biases to the trial (assume that any response to being interviewed is the same between the SC and VEM groups), interviewing ongoing trial patients about their experience of acute stroke care (which will include

mobilisation) after the intervention period may be a possibility. Collaboration between the developers, the providers and the intended population of VEM is an important consideration for the future.

Lessons can be learnt from hospitals that have and have not implemented other acute interventions successfully. Healthcare professionals' views and experiences of change were explored; however the detail that could be divulged was limited due to time-constraints. A closer evaluation of the real-life workability of thrombolysis could provide transferable information for the implementation of VEM. How tasks are allocated and how the flexible staffing structure (as raised when discussing thrombolysis in this study) is initiated and operated when a patient eligible for thrombolysis arrives on the ward are aspects which could be studied.

Developing implementation strategies

Better, more broad implementation and uptake leads to better outcomes.[41] The transfer of effective programs into the real world is challenging and is considered to comprise of four phases including "how well information about a program's existence and value is supplied to communities (dissemination), whether the local community decides to try the new guideline (adoption), how well the programme is conducted during the trial (implementation) and whether the programme can be maintained (sustainability)." [41] There is a need for implementation strategies that are evidence-based to facilitate each of these phases. Although, the development of implementation strategies usually occurs in the later stages of the implementation process[36] some preliminary recommendations for the implementation of VEM for each of these four phases are provided. Each stage is broadly defined and preceded by key findings from this qualitative study to illustrate that an evidence-based approach to generating these recommendations has been used.

Dissemination

Dissemination refers to how well information about an intervention's existence and its value reaches its users. This process is defined as the spread of new ideas

and technologies. They must be marketed effectively so that the target audience learn about its existence and potential benefit.[197]

Key findings relating to the dissemination stage:

- Healthcare professionals have concerns about the feasibility of implementing very early mobilisation in real-life
- Healthcare professionals believed that very early mobilisation may result in care being compromised for certain groups of patients
- Pre-existing contextual factors may facilitate the implementation of very early mobilisation; regular and early team communication, planning the patient's day, collaboration as characterised by non-hierarchical relationships amongst participants, mutual trust and open communication, shared responsibilities for completing tasks and efforts to reach consensus when opinions are conflicting

Recommendations for the dissemination stage:

- Initiate priming activities to highlight the need for and to trigger change such as provide feedback to staff on findings from local behavioural mapping studies studying context and current practices
- Provision of a guideline with clear statement to define and provide a set of actions to distinguish very early mobilisation from standard practice
- Provide a statement to address concerns about equity of care. The use of negative recommendations may be required to reinforce and reason why certain groups of patients may not benefit i.e. 'the use of very early mobilisation is *not* indicated for patients with…'
- Appoint trouble-shooters and scientists specialising in behavioural change to work with hospital staff at all levels to identify potential problems and provide solutions at this early stage

Adoption

This refers to whether the user decides to try the new intervention. For any practice to be adopted in clinical practice there is a need for those that are providing it to be convinced that the work is worth the effort. Individuals need to believe that the benefit of changing practice is 'worth' the energy and resources to make the change. Facilitation is emerging as a way in which to encourage evidence uptake in healthcare and successful implementation is dependent on the quality of the facilitation.[198] Facilitation is a technique by which one person makes things easier for others.[199] Facilitators play an important role in assisting individuals and teams with identifying what needs to change and how to embed these changes into real life. The existence of a facilitator has been recognised as a valuable resource to encouraging new ways of working and thinking.[41] Facilitator appears to be the new buzzword for champion, no attempt has been found in the literature to distinguish between these terms so they are used interchangeably here.

Key findings relating to the adoption stage:

- Healthcare professionals often relied on success stories (using thrombolysis as an example) from colleagues working at other hospitals or research findings
- Change needs to be planned in advance, introduced in stages with everyone on-board at an early stage
- Healthcare professionals were more likely to engage in the change if it had 'appeal' i.e. there was a sense that 'everyone is talking about it', offered new responsibilities or had visible and immediate effects on patients
- Some hospitals were more cautious in adopting change, preferring to see how other hospitals got on first before trying it themselves

There were differences in how professional groups responded and approached change. There was a sense that doctors, with more experience of being the leaders in change, were more proactive whilst therapists and nurses were more tentative about how they may overcome barriers (Appendix 16). Generally, the

use of a champion was seen to have advantages and disadvantages. Given the multidisciplinary nature of VEM this may not be the most appropriate approach to getting everyone on-board. A champion was seen to have a role to play in solving problems and maintaining enthusiasm in order to sustain the change. Having one dedicated person overseeing and co-ordinating the process may become onerous for the champion and result in the rest of the team becoming evasive. Therefore, the success of this approach lies in having the organisation onboard and everyone receptive to change.

Recommendations for the adoption stage:

- Efforts to break negative preconceptions about the intervention i.e. perceived workload may be more attributed to participation in a study requiring more time than delivering the intervention in real-life due to the study administration and additional measurements that may need to be taken. The trial protocol may differ from the final product recommended for use in real-life.
- The risks and benefits of very early mobilisation are explicitly stated with easily interpretable scientific findings
- The appointment of a leader with dedicated time to encourage 'buy-in' may be just as effective as the use of an individual as a champion. This should be at the discretion of each hospital.

Implementation

Implementation refers to how well the intervention was conducted during the trial and if evaluates positively, how well it will be implemented in real-life post evaluation. Early monitoring of implementation during and post-trial can identify problems in application that can be corrected. Early monitoring of implementation followed by retraining has doubled fidelity of implementation to over 85% for providers who were having initial difficulties.[200] Adaption of an intervention prior to and during its implementation is a controversial issue.[28] Some believe that it is acceptable to adapt the intervention, determining to what extent original core program components can be changed, whether new

aspects are added and what they are, or whether parts of the intended intervention are omitted.

Key findings relating to the implementation stage:

- Healthcare professionals previous experience of the intervention within the trial and changes in practice that they have been involved in may be an important predictor to successful implementation
- The process of normalisation was a concept that many staff related to whereby new practices became routine and cumulative experiences of the new intervention or change alleviated fears associated with the introduction of the intervention

Healthcare professionals did not routinely discuss as a team the process of implementation to identify problem areas or solutions. When asked about the use of process evaluation meetings this was well received with staff seeing benefits in ironing out any issues, identifying any slippage and having time within the working day to discuss as a team problem areas and solutions. Meetings would also provide a platform to support, put anxieties into perspective and learn from each other.

Recommendations for the implementation stage:

- Provide example models for local delivery which may be based on current and future development of staff skill-base and structures such as the availability of equipment
- Education packages underlining the benefit and risks of very early mobilisation. Those that recognise the need for the intervention, the potential benefits, have self-efficacy and skill proficiency are more likely to implement a program with higher levels of adherence
- Systems to actively identify eligible patients. This is an important practice which will involve organisational collaboration as well as individual ownership

- Protocol or decision flowchart should consist of a task checklist of which some may relate to contextual issues– Has this been verbally communicated to the nurse? If applicable, has the bed-side mobility chart been updated?
- Risk management strategies which target pre-existing beliefs such as the need for patient medical stability prior to mobilisation
- Early morning team communication to plan and structure the patient's day
- Embed 'mini' process evaluations in team meetings. Formally referred to as quality circles these are more readily used in industry than healthcare. Quality circles are defined by voluntary participation, collaborative decision making and contribution from employees.[201]
- Generally, implementation strategies should reflect the acute and busy environment of ASUs and take on-board the factors that are likely to influence behavioural change in HCPs (such as preconceptions around patient eligibility, the benefit of the intervention to the patient, the effort required by the individual to make the change).

Sustainability

Sustainability refers to whether the intervention can be maintained in the long-term. It has been shown that few interventions are sustained over time, regardless of the success achieved during the trial. Sites may adopt the practice but it is also vital to monitor how these are being sustained in the long-term. Healthcare is delivered in dynamic systems with changes in the workface, high turnover of staff, new interventions and changes in the population therefore there is a need to monitor the implementation of these contextual factors and a mixture of observational techniques and interviews should be integral to the longer term monitoring plan. Strong leadership and the day-to-day presence of the leader are key, with time dedicated within portfolios to allow staff performance to be monitored and developed.

Key finding relating to sustainability:

- Feedback sometimes resulted in staff feeling threatened by the need to respond to performance criteria. Feedback itself may not explain why things are not being achieved. For example, recording information about actions that did or did not happen does not explain the clinical context in which this did or did not occur.

Recommendations for the sustainability stage:

- Include process indicators related to very early mobilisation in quality assurance activities
- Engage and involve staff in the monitoring process which may involve a general change in the way audits are conducted. Healthcare professionals need to view actual practice data about their performance and context. Video recording would provide the ideal data.
- Engage with professional councils to support and campaign for the continued development of seven-day working (extended day and shift system) for therapists

5.5 Conclusion

This Chapter includes research that addresses the evaluation stage of the Medical Research Council complex intervention framework. This study has provided data on current stroke processes, pre-existing context and the factors that may influence the future implementation of very early mobilisation (VEM). It has also provided rich data about the complex array of individual, intervention specific and environmental elements that influence change. A set of beliefs has been formulated based on the viewpoints of a range of healthcare professionals with and without experience of implementing VEM within a trial setting. Barriers were complex, multifunctional and affected the system at a number of levels; the individual healthcare professional, patient, social, organisational, political and economic. Access to the patient within 24 hours and medical instability were the barriers most frequently mentioned. The hospital organisational

structure often impacted on the speed of patient diagnosis and subsequent pathway to the acute stroke unit. The intervention's association with increased staff workload was a constant theme throughout discussions. This study has highlighted the need for a well-designed implementation plan and strategies which aim to have staff 'on-board' and one that breeds a supportive management climate to ensure the successful implementation of VEM.

6 Economic impact of very early mobilisation

6.1 Introduction

Much of the onus of stroke care lies with the rehabilitation service and since stroke rehabilitation is highly resource-intensive, it is important for policy makers to consider the potential trade-offs between all relevant costs and benefits. Chapter 4 estimated the clinical impact of VEM showing that it has the potential to improve outcomes after stroke. However, the cost-effectiveness of VEM has not yet been estimated or the economic impact explored. Therefore, this Chapter aims to estimate the cost-effectiveness of VEM.

A number of systematic reviews to identify the economic evidence in stroke research have been conducted;[202-205] however only one was dedicated to rehabilitation services. The studies included in these reviews were appraised based on good practice guidelines for economic evaluation alongside clinical trials and economic modelling.[206 207] The authors of these reviews made several general suggestions to improve the undertaking of economic evaluation in stroke, although these are not specific to complex rehabilitation interventions. These include: the comparison of all relevant interventions, taking account of all available sources to ensure the reliability of effectiveness and cost data and examining the uncertainty of the results.

The clinical evaluation of a complex intervention such as stroke rehabilitation service is widely recognised as more complicated (Chapter 1) than that of, say, pharmacological interventions. It is therefore not unreasonable to state that the economic evaluation of a complex intervention may be more challenging; the context dependent and variable nature of complex interventions is a complicated arena for researchers undertaking economic evaluations and one that deserves attention. Therefore, this Chapter begins with a systematic review aimed to identify approaches used to evaluate the cost-effectiveness of stroke rehabilitation. The findings from this review will then be used to inform the economic evaluation of VEM. The resource use items and the health-related quality of life data reported in Chapter 4 will now be used in this economic evaluation. The qualitative evidence from Chapter 5 with regards to the

suggested implementation strategies for VEM will also be considered to identify costs not traditionally associated with the implementation of complex interventions.

6.1.1 Types of economic evaluation

An economic evaluation must compare two or more alternatives, examining both the costs and consequences.[208] A number of different types of economic evaluations can be used to evaluate health interventions depending on the aim of evaluation and in some cases the data available. As these will be referred to and used throughout this Chapter the various types of economic evaluations, along with the health economics terminology used, will now be introduced and briefly explained.

The types of economic evaluations that will be referred to in this Chapter are as follows: cost-minimisation analysis (CMA), cost-consequence analysis (CCA), cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) (Table 6-1). The other type of economic evaluation is a cost-benefit analysis (CBA) which will not be referred to throughout this Chapter. A CMA is conducted when there is no difference in effect therefore only costs are of interest. A CCA is a balance sheet approach where all costs and all consequences are tabulated but not combined. A CEA synthesises cost and effect data in the form of an incremental cost-effectiveness ratio (ICER) which identifies the additional costs associated with the intervention per additional unit of outcome produced by the intervention in comparison to the alternative. A CUA is sub-type of a CEA and is used where there is no single outcome of interest. A CBA is where all inputs (i.e. healthcare resources and costs) and outputs (health outcomes) are expressed in money terms.

Table 6-1 Types of economic evaluation

Study type	Key feature(s)	Measurement of effectiveness	Cost-outcome comparison
Cost-minimisation analysis	• Presents costs and resource • Conducted when there is no difference in effect	• Benefits are equivalent	• None
Cost-consequence analysis	• Tabulates all costs and all consequences separately i.e. a 'balance sheet' approach	• Benefits are multiple	• None
Cost-effectiveness analysis	• Combines the costs with primary natural unit of interest	• Natural units (e.g. death, falls, life-years gained)	• Cost per outcome unit
Cost-utility analysis	• Combines the costs with a measure of utility	• Healthy years (e.g. quality adjusted life years)	• Cost per QALY
Cost-benefit analysis	• Both inputs and outputs are expressed in monetary terms	• Monetary benefits	• Net monetary benefit

Adapted from Drummond and Jefferson, British Medical Journal[206]

The measure of effectiveness in a CEA is specific to the intervention in terms of the intervention's natural units. Therefore, it does not allow a comparison of cost-effectiveness to be made between different interventions in other areas. To allow such comparisons to be made by decision makers a generic measure of effectiveness is required. A QALY is one that is commonly used in the economic evaluation of health interventions, this is also the preferred measure by NICE.[209]

A QALY is a measure of combined length of life and health-related quality of life (valued on an index where 1 represents perfect health and 0 represents death) in a single outcome. Quality-adjusted life years adjust each remaining year of a person's life by the expected health-related quality of life for those years. For example, a patient aged 60 years of age may be expected to live for another 20 years, however, having had a stroke their HRQoL is expected to be half the quality of life prior to stroke for the remainder of their life. Therefore, at the patient's current age of 60 years, this patient has 10 QALYs remaining (20 years x 0.5 QALY/years). Within a trial setting the patient's actual HRQoL can be collected at intervals during the trial and at follow-up. The HRQoL data can then be used to estimate HRQoL beyond the observed time frame of the trial i.e. for ten years or a life-time.

In the UK, the standard threshold set by NICE to assess whether or not an intervention is cost-effective is based on the value that society places on a QALY. These values are in the region of £20,000 to £30,000.[210]

Aim

The aim of this Chapter was to use an evidence synthesis approach to model the economic impact of VEM using the findings of a systematic review and the IPD from VERITAS and AVERT phase II to inform the model.

6.2 Systematic review of economic evaluations

6.2.1 Methods

A systematic review was undertaken prior to the economic evaluation to review the methodological approaches and assess the quality of economic evaluations in stroke rehabilitation. As the findings of the systematic review will inform the methods of the economic evaluation the methods and findings of the systematic review are presented before the economic evaluation.

Inclusion and exclusion criteria

Studies that reported on economic evaluations of rehabilitation interventions targeted at stroke patients were included. A stroke rehabilitation intervention was defined as either a service (acute/community rehabilitation or early-supported discharge) or a specific intervention aimed at improving the patients activity such as walking and participation in, for example, leisure activities and employment after stroke. Economic evaluations were defined as studies that compared two or more alternative stroke rehabilitation interventions or services with the costs and outcomes being examined for each alternative. Studies that were methodological or discursive, reviews of economic evaluations, efficacy/effectiveness evaluations, studies that presented resource use only without unit costs, cost studies where no consequences/benefits were reported or evaluated the burden of disease were excluded. Rehabilitation interventions that included a drug or medical device, or interventions or services targeted at

carers and/or HCPs were also excluded.

Search strategy and data extraction

The following electronic databases were searched from inception to September 2011: EMBASE, MEDLINE In-Process and NHS Economic Evaluation Database (NHS EED). No restrictions were applied to language. In order to identify relevant studies, search strategies specific to each database were developed using a combination of MeSH and free text words (Appendix 17). A citation search of Web of Science and reviewing the references lists of key papers was undertaken to ensure an efficient and comprehensive coverage. The titles and abstracts of retrieved references from the search were screened by the author only to exclude irrelevant studies. The full-text articles of studies that satisfied the inclusion criteria were reviewed in full and data extracted. Decisions were then cross-checked with a Health Economist. Data extraction included key study and methodological characteristics:

- The intervention or service and the comparator(s) used
- The perspective and time horizon of the evaluation
- The source of effectiveness and cost data
- The measure of benefits (such as natural units, utility based measures or monetary benefits)
- The measure of cost-effectiveness (such as incremental cost per QALY or incremental cost per life year gained)
- Reported analysis of uncertainty

The quality of each of the studies was assessed using a well-defined checklist for the conduct and reporting of economic evaluations.[206] The findings from this quality assessment were summarised using the following three headings; study design, validity of data and analysis and interpretation of results.

6.2.2 Results

The total number of studies identified by the search was 2,061. Following screening of titles and abstracts the full-text articles of 35 studies were assessed in detail (Appendix 18). Overall, 21 studies met the selection criteria, and were included in the review (Appendix 19).[211-231] The results from the quality assessment are shown in Appendix 20 to Appendix 22.

Study design

Overall, nine studies used a CCA type approach, six studies conducted a CEA and the remaining six were classified as a cost-minimisation analysis (CMA). None of studies conducted a CUA or developed an economic model i.e. to extrapolate beyond the timeframe of the trial. There was variation between the studies that adopted a CCA approach in relation to the planning, design and conduct of the evaluation as well as the reporting of all costs and all consequences. None of the studies provided a rationale for adopting this cost-consequence approach and this was not explicitly stated as the type of economic evaluation in any of the studies. All possible consequences of the intervention were not identified and/or tabulated alongside all possible costs, with the reader often being referred elsewhere for the effectiveness results of the study. One of these studies was a health technology assessment where data from the individual studies were extracted and synthesised.[220] Cost-minimisation analyses were conducted where it was inappropriate to synthesis the costs and benefits as there had been no difference in effect.

Overall, the perspective, when reported, was that of the healthcare provider. Two studies adopted a societal approach whereby productivity costs were included.[225 229] All studies followed patients for either six months or one year with the time horizon for the economic evaluation rarely stated explicitly.

Validity of data

In eighteen studies, clinical effectiveness data were from RCTs in which between 59 and 331 stroke patients were recruited. The majority of studies investigated a

stroke rehabilitation service including early supported discharge service, community or home-based rehabilitation. One study evaluated a specific stroke rehabilitation intervention.[225] The comparator was always current practice within the particular setting. All studies provided some description of the intervention under study; however, the level of detail with respect to the staffing structure, content and quantity of rehabilitation sessions provided varied.

The number and type of patient-related outcomes reported in the studies reflects the multidimensional nature of stroke rehabilitation in its aim to affect the level of impairments such as lost motor function, activity limitations and participation restriction.[20] All studies reported more than one patient-related outcome, four studies[211 212 217 231] reported carer-related outcomes such as carer stress and five studies[211 212 215 216 228] reported either patient or carer satisfaction with the health care that they had received. With respect to HRQoL, the measure used to derive QALYs for use in economic evaluations, the majority of studies reported an overall non-significant effect. One study showed significant differences in the overall HRQoL score [224] while three other studies reported improvements for specific domains (most commonly the physical component) of the HRQoL assessment.[217 226 228]

Costing was limited to the delivery of the intervention in two studies [213 230] and did not include non hospital resource use such as community services provided. In one study assumptions regarding intervention delivery and/or resource use were made as opposed to being solely informed by data from the individual patients included in the study. It was explicitly stated in two studies that an average cost was applied where patients that had no or incomplete information about resource use. [211 213] The resource use items associated with the service or intervention under evaluation were described in detail, but in nine studies resource quantities were not always given separately.[214 215 217 218 223 224 226-228] The sources used to determine resource use varied and all studies included specifically designed study questionnaires/interviews or hospital departmental records. In all cases the method of costing included the use of data from hospital expenditure or the application of national unit costs. Only one study considered the costs of implementation which included those associated with establishing

new links with other agencies and increased administration.[221] Overall, costs to the patient i.e. 'out-of-pocket' expenses such as home adaption's or equipment purchased were not identified in the majority of studies (n=17) whilst costs to informal carers were identified as potential costs in three studies but this rarely measured. Authors of one study stated that they had attempted to incorporate costs to the informal carer but questioned the quality of their data.[212]

Analysis and interpretation of results

Where an ICER was calculated the measure of effectiveness was in natural units such as cost per good outcome,[150] cost per disability averted [224] or cost per mean point improvement in balance.[218] The impact of variations in resource use or unit costs, on the final results, was analysed in seven studies. Sensitivity analysis tested assumptions around average per-day costs,[211] length of stay,[212] therapy workload,[222] provision of a home-based rehabilitation team,[211 222 224] ambulance costs[222] and day hospital.[222] One study used probabilistic sensitivity analysis to examine the uncertainty of ICER calculated.[225] One study explored the opportunity costs that an early discharge team may have on increasing inpatient bed-capacity.[212]

Summary of limitations

Assessing the quality of the studies against the generic quality checklist identified some general methodological shortcomings in the economic evaluations, such as not routinely conducting uncertainty analysis or not justifying the design of the study. There were other shortcomings that are of particular relevance to the evaluation of complex interventions, with regards to the context and patient dependent nature of such interventions. These will now be identified and explained below:

The perspective of the evaluation was not explicitly stated - this makes it difficult to assess if all the appropriate costs and outcomes have been identified, measured and valued. Where it was stated, the majority of studies adopted a healthcare perspective, therefore did not routinely measure and value costs associated with a loss of productivity and informal care. This has particular

relevance in the study of complex interventions where the aim is often to rehabilitate the person to return home or return to work. Therefore, a broader societal perspective, which considers a range of costs and effects is recommended over a narrower perspective i.e. health service.

A protocol-driven approach to costing intervention implementation - this requires assumptions about what resources were actually used and that the intervention was delivered as intended. This may not be true as complex interventions involve different resources to tailor the intervention to the needs of individual patients.

Inadequate attempts to synthesis the cost and effectiveness data - where studies did not aggregate costs and effects in the form of an ICER few authors used narrative synthesis to provide a statement about the cost-effectiveness of the intervention or systematically tabulate all costs and consequences. Out of the studies that did present cost-effectiveness in the form of an ICER, three studies reported an ICER for all clinical outcomes.

Cost-utility analysis was not an approach used in any of the studies - none of the studies attempted to value the HRQoL data, either because this was not collected during the trial or the intervention had no effect on quality of life. As a CUA is the preferred type of analysis by decision makers this will limit the comparisons that can be drawn between interventions from other disease areas. It has been argued that QALYs do not capture all the broader benefits (including non-health benefits) that are associated with complex interventions[232], although this argument was not used to justify the approach used in any of the studies.

6.3 Economic evaluation of very early mobilisation

6.3.1 Methods

Study design and perspective

As the potential outcomes of stroke rehabilitation are likely to be wide-reaching with implications for patients, carers and society, and as supported by the findings of the systematic review, the perspective of the economic evaluation

was societal. Very early mobilisation was the intervention and the comparator was SC. A CCA was conducted in the first instance where all costs and consequences of the intervention were tabulated. The use of a CCA is advantageous when the rehabilitation intervention is known to have multiple health and non-health benefits and one composite measure is justifiably inappropriate. The costs and consequences of VEM were identified using the findings from the systematic review, the IPD MA (Chapter 4) and the qualitative process evaluation (Chapter 5). As previously indicated in the IPD meta-analysis, VEM may have more specific health benefits such as increased odds of independence other than those captured by measuring general HRQoL. With this in mind (and as supported by the findings from the systematic review) CEAs using independence and immobility-related complications as the natural measures of effectiveness were conducted so as to fully explore all possible benefits/outcomes of VEM in comparison to SC. Cost-utility analysis is the preferred type of economic analysis by NICE who are the UK decision makers with regards to health technologies. Therefore, a complimentary CUA was conducted. The primary outcome for the CUA was the incremental cost per additional QALY gained. The calculation of QALYs was estimated using trial data.

Measurement and valuation of effectiveness

The primary effectiveness outcome for the CEA was the incremental cost per additional case of independence gained. The secondary effectiveness outcome for the CEA was the incremental cost per additional immobility-related complication prevented. All effectiveness data were based on the IPD meta-analysis. The HRQoL data as collected using the AQoL instrument was previously summed to provide an overall unweighted HRQoL-index (Chapter 4). The AQoL score was then used to compute an overall utility score weighted by preference (using a widely available algorithm[233]) in order to calculate QALYs for use in the CUA. To calculate a within trial QALY requires HRQoL data to be collected at baseline and at one or more follow-up points.[234] Health-related quality of life data was not collected at baseline, therefore, QALYs were calculated based on the three month and 12 month HRQoL data from AVERT phase II using a standard approach.[234] Values were not assigned to the natural units of effect.

Measurement and valuation of costs

Costs and resource use are likely to vary between countries due to differences in unit costs and the different combinations of resource use that are required to deliver the intervention within a given setting.[235] Therefore, it was considered inappropriate to combine the UK and Australian resource data, so for this reason the CEA was based on the VERITAS resource use data. Resource use was classified into one of the following three sectors; health care, personal or societal. Health care resource use included NHS resources and those consumed in the community, as well as immobility-related complications (adverse events considered to be related to the intervention). Data about implementing the intervention (such as staff time) were not collected in the VERITAS study. Therefore, it was assumed that the implementation of the intervention was per protocol which aimed at doubling current therapy time. Current therapy time as provided in the UK has been estimated to be approximately 45 minutes.[106 236] Loss of productivity was not measured in VERITAS, therefore it was estimated based on that measured in AVERT phase II. The mean loss of productivity was 30 hours per week for SC patients with no loss of productivity for patients in the VEM group at three months.[150]

The costs were calculated by applying a unit cost to each of the resource items. The reference year for costing was 2010 (£UK). Unit costs were based on UK National Health Service reference costs.[237] It is not appropriate to divide total health care expenditure by the number of patients as it does not account for individual patient differences (case-mix). Reference costs use case-mix adjusted measures and in the UK these are called health care resource groups. These groups are "defined by clinicians and reflect clinical practice in the UK, providing standard groupings or similar treatments that use similar resources." [238] Where reference costs were not available, Personal Social Services Research Unit costs were applied.[239] The Personal Social Services Research Unit costs were used to cost staff time, community visits made by a home help and GP visits. Staff time (based on cost per hour for an Agenda for Change Grade 5 Physiotherapist) was used to cost the implementation of VEM per protocol and SC. Individual patient costs were summed and the difference in mean costs between the VEM and SC groups was calculated as recommended.[240] The mean

number of visits made by informal carers was measured in VERITAS.

Informal care (time of informal carers) was valued on the equivalent hourly rate of a local authority home care worker. Each visit by the informal carer was assumed to last one hour. Productivity costs were presented separately and valued according to UK earnings from the National Office of Statistics. Excluding overtime, median hourly earnings of full-time employees on adult rates of pay were £12.50 per hour in April 2010.[241] The mean loss in productivity for the SC group was calculated as follows: 30 hours multiplied by £12.50 multiplied by 12 weeks.

Data analysis

All costs and consequences were tabulated. Costs were listed according to perspective (health care, personal or societal). For the CEA and the CUA the cost and effectiveness data were used to calculate an ICER (ICER = incremental cost divided by the incremental unit of outcome). In health economics, dominance is the term used to describe a situation where an option is both more costly and less effective than the alternative intervention.[242] For example, on comparing two interventions, if intervention A is less costly and more effective than intervention B, intervention B is said to be dominated by intervention A. Where dominance is found no ICER is reported, the outcome is dominance.

Sensitivity analysis

One-way sensitivity analyses were performed on key unit costs by varying one measure at a time. As this was intended as a small scale evaluation the sensitivity analysis was limited to costs and to the CEA using independence as the main outcome as per the IPD. The unit costs that were varied included the hourly rate of a physiotherapist, home carer and informal carer which were increased by 50% then by 75%. As actual resource use associated with the intervention was measured in AVERT phase II (time spent in therapy) and the methods to costs informal carers time vary [243], additional sensitivity analyses were undertaken to assess the impact on cost-effectiveness outcomes. These included; i) costing physiotherapist time based on the actual mean time spent in

therapy for the SC and VEM groups (17.3 minutes and 40.3 minutes, respectively[150]) ii) costing the intervention based on nurse time iii) costing the need for an informal carer equivalent to admission to a local authority care home.

6.3.2 Results

Results of cost-consequence analysis

The costs (health sector, personal and societal) are shown in Table 6-2 (for resource quantities refer back to Chapter 4). When only costs associated with healthcare are included the mean cost for a patient in the VEM group was higher than for a patient in the SC group (£4248 versus £3803). The two key resource items which contribute to this difference in cost between the two groups are the implementation of the intervention and resource use associated with deep venous thrombosis. When the costs associated with the loss of productivity are included the mean cost for a patient in the VEM group was lower than for a patient in the SC group (£5975 versus £8444).

In addition to the resource use items listed, there are likely to be costs associated with implementation strategies used to embed VEM into routine practice. Although there was not a consensus from staff regarding the most appropriate implementation strategy for VEM most staff viewed the provision of educational sessions as a key facilitator to implementing VEM by HCPs. Therefore, costs identified with the provision of such sessions; including educational materials (printing and/or videos), personnel (expert speakers and a facilitator) and the opportunity costs of staff attending the sessions (and learning time) should be considered.

Table 6-2 Costs of very early mobilisation

Costs of very early mobilisation in comparison to standard care						
Resource item	**Unit**	**Unit cost**	**Unit cost source**	**SC (n=16) (mean cost)**	**VEM (n=16) (mean cost)**	**Data source[1]**
Health care sector						
Implementation of intervention	Hour	£40	PSSRU	£189 (47)	£360 (96)	VERITAS
Acute-phase hospitalisation	National los	£2793	NHS Reference cost	£2793	£2793	VERITAS
Immobility-related complications (baseline-day 5)						VERITAS
• chest infection	Event	£1028	NHS Reference cost	£514 (650)	£129 (351)	VERITAS
• urinary tract infection	Event	£1380	NHS Reference cost	£259 (556)	£0 (0)	VERITAS
• deep venous thrombosis	Event	£1376	NHS Reference cost	£86 (344)	£0 (0)	VERITAS
Immobility-related complications (day 5-month 3)						VERITAS
• chest infection	Event	£1028		£0 (0)	£64 (257)	VERITAS
• urinary tract infection	Event	£1380		£173 (471)	£172 (471)	VERITAS
• deep venous thrombosis	Event	£1376		£0 (0)	£86 (344)	VERITAS
District nurse visit	Visit	£36	NHS Reference cost	£0 (0)	£0 (0)	VERITAS
GP visit	Visit	£36	PSSRU	£84 (186)	£79 (88)	VERITAS
Physiotherapy visit	Visit	£99	NHS Reference cost	£304 (647)	£185 (386)	VERITAS
OT visit	Visit	£99	NHS Reference cost	£304 (540)	£111 (345)	VERITAS
Social services						VERITAS
Home help visit	Hour	£25	PSSRU	£40 (135)	£397(1440)	VERITAS
Mean cost per patient (healthcare costs only)				£3803 (930)	£4248 (1587)	-
Personal costs						VERITAS
Informal carer visited	Hour	£25	PSSRU	£161 (283)	£1727(6006)	VERITAS
Mean cost per patient (healthcare and personal costs)				£3944 (938)	£5975(6883)	-
Societal costs						
Productivity loss	Hour	£12.50	ONS	£4500	£0 (0)	AVERT phase II
Estimated mean cost per patient (with productivity cost)				£8444	£5975	-

The health-related consequences for the patient (both short and long term) and carer are shown in Table 6-3 and have been discussed more fully in Chapter 4. At one week the risk of experiencing immobility-related complications for VEM patients remained significantly lower than that of SC patients. At three months patients who underwent VEM were three times more likely to be independent, had a increased chance of non-impaired mobility and significant improvement in ADL than SC patients.

The systematic review highlighted that stroke rehabilitation may not only have health benefits but also non-health benefits and these may include:

- Promoting the patient's return to work (improved productivity of the workforce; reduced use of government benefit schemes)
- Increased satisfaction with aspects of the delivery of health care
- Increased knowledge; acute rehabilitation interventions may provide pressure for more public health campaigns aimed at increasing the general public's recognition of the symptoms of stroke

Table 6-3 Consequences of very early mobilisation

Consequences of very early mobilisation in comparison to standard care				
Health-related	**Effect**	**Estimate (95%CI)**	**p-value**	**Data source***
Patient outcomes (day 5-7)				
Stroke severity	Non-significant reduction	-0.59 (-2.44, 1.27)	0.53	IPD MA
Immobility-related complications	Significant reduction	0.23 (0.07, 0.71)	0.01	IPD MA
Excessive fatigue	Non-significant reduction	0.79 (0.27, 2.31)	0.67	IPD MA
Patient outcomes (month 3)				
Level of independence	Significant improvement	3.11 (1.03, 9.33)	0.04	
Immobility-related complications	Non-significant reduction	0.55 (0.23, 1.32)	0.42	IPD MA
Discharge home	Non-significant increase	1.40 (0.46, 4.30)	0.60	IPD MA
Non-impaired mobility	Significant increase	7.81 (1.70, 35.00)	0.01	IPD MA
Death	Non-significant reduction	0.93 (1.11, 7.90)	0.95	IPD MA
Independence in activities of daily living	Significant improvement	4.20 (1.34, 13.50)	0.01	IPD MA
Health-related quality of life	Non-significant increase	-3.63 (-7.30, 0.13)	0.06	IPD MA
Carer outcomes				
Carer strain	Non-significant reduction[215]	-	0.17	SR

* IPD MA = Individual patient data meta-analysis, Chapter 4; SR = Systematic review (data extracted from the review is not specific to very early mobilisation), Chapter 6

Results of cost-effectiveness analyses

Details of the mean costs, effectiveness and cost-effectiveness expressed as an ICER are provided in Table 6-4. From a societal perspective, as VEM was less costly and more effective, it was found to dominate SC, therefore no ICER was reported. When excluding societal costs to consider healthcare and personal costs only, the VEM intervention resulted in an additional 10 patients achieving independence at an additional cost of £2031. Therefore, the ICER associated with VEM in comparison to SC was an additional £203 per additional patient achieving independence. As the incremental outcome is the same for immobility-related complications as for independence, the ICER associated with VEM in comparison to SC remained the same. These ICERs suggest that VEM is potentially cost-effective when considering the NICE threshold of £20,000 to £30,000.

Table 6-4 Results for cost-effectiveness analysis

Societal perspective

	Mean cost	EA	ICER	EB	ICER
SC	£8444	17	-	17	-
VEM	£5975	27	Dominates*	7	Dominates

Healthcare perspective

	Mean cost	EA	ICER	EB	ICER
SC	£3944	17	-	17	-
VEM	£5975	27	£203	7	£203

E^A = effectiveness outcome is independence
E^B = effectiveness outcome is immobility-related complications
* The term 'dominates' refers to the treatment strategy that is less costly and more effective. In this case SC is dominated by VEM.
ICER; Incremental cost-effectiveness ratio

Cost-effectiveness outcomes were not sensitive to varying unit costs for the implementation of the intervention, home help or informal carer time (Table 6-5). Cost-effectiveness outcomes were not affected when different estimates were used to cost the intervention. Outcomes were sensitive on costing informal care equivalent to a local authority sheltered housing weekly rate.

Table 6-5 Sensitivity analyses for costs

Resource category	SC Mean cost (SD)	VEM Mean cost (SD)	Difference in cost (95% CI)	p-value	ICER
Baseline analysis	£3944 (939)	£5975 (6883)	£2031 (-1515, 5578)	0.25	203
Sensitivity analysis					
Implementation intervention costs at 50% of baseline	£4039 (950)	£6155 (6863)	£2116 (-1420, 5654)	0.23	212
Implementation intervention costs at 75% of baseline	£4086 (955)	£6245 (6853)	£2159 (-1374, 5692)	0.22	216
Home help unit costs at 50% of baseline	£3963 (967)	£6173 (7020)	£2211 (-1407, 5829)	0.22	221
Home help unit costs at 75% of baseline	£3972 (983)	£6273 (7116)	£2301 (-1367, 5968)	0.21	230
Informal carer unit costs at 50% of baseline	£4042 (1015)	£7139 (9990)	£3094 (-2033, 8220)	0.23	309
Informal carer unit costs at 75% of baseline	£4078 (1037)	£7568 (11452)	£3490 (-2381, 9361)	0.23	349
Implementation intervention costs based on AVERT phase II	£3827 (925)	£5777 (6906)	£1949 (-1608, 5506)	0.27	195
Implementation intervention based on nurse time*	£4001 (945)	£6083 (6871)	£2082 (-1459, 5623)	0.24	208
Informal carer costs equivalent to local authority sheltered home**	£5342 (2190)	£5127 (2936)	£-214 (-2084, 1656)	0.82	Dominates***

Unit costs;

* Nurse hourly rate = £52

** Expected total costs of local authority home care for older people = £293/week

*** The term 'dominates' refers to the treatment strategy that is less costly and more effective. In this case SC is dominated by VEM.

Primary effectiveness outcome was used (independence at 3 months)

Result of cost-utility analysis

Details of the mean costs, effectiveness and cost-effectiveness expressed as an ICER are provided in Table 6-6. From a societal perspective, the ICER associated with VEM in comparison to SC was an additional £256,900 per additional QALY. The ICERs suggest that VEM is potentially not cost-effective when considering the NICE threshold of £20,000 to £30,000. When excluding societal costs to consider healthcare and personal costs only, VEM was associated with a higher cost and lower effectiveness than SC, so it is therefore said to be dominated by SC.

Table 6-6 Results for cost-utility analysis

Societal perspective			
	Mean cost	**E[A]**	**ICER**
SC	£8444	0.51 (0.42)	-
VEM	£5975	0.50 (0.50)	£246,900
Healthcare perspective			
	Mean cost	**EA**	**ICER**
SC	£3944	0.51 (0.42)	Dominates*
VEM	£5975	0.50 (0.50)	-

EA = effectiveness outcome is independence

* The term 'dominates' refers to the treatment strategy that is less costly and more effective. In this case SC is dominated by VEM.

ICER; Incremental cost-effectiveness ratio

6.4 Discussion

Summary of key findings: systematic review

This systematic review included 21 studies that had conducted an economic evaluation of a stroke rehabilitation service or specific intervention in comparison to current care. The findings from the quality assessment highlighted some general methodological shortcomings of economic evaluations conducted in this area. These included not reporting resource quantities and costs separately or examining uncertainty. Further limitations, that may have more implications for the economic evaluation of stroke rehabilitation, were also identified such as the perspective of the evaluation was not explicitly stated and inadequate attempts to synthesise the cost and effectiveness data.

As the majority of studies did not present the costs and benefits in an aggregate form it was difficult to identify the primary outcome used in some of the studies. This was appraised on the appropriateness of the outcome in relation to the type of evaluation conducted. It may be that the generic nature of the checklist was limited in representing some of the issues relating to the study of complex interventions such as the multiple outcomes and scope to justify why costs and benefits were not aggregated. That said, the majority of these studies were inadequate in identifying, measuring and valuing all costs and benefits pertinent to the complexity of stroke rehabilitation. There was little consideration given to the wider effects of stroke rehabilitation such as productivity costs, patient education and the impact on carers.

Summary of key findings: economic evaluation

As recommended by the MRC complex intervention framework this economic evaluation is an early stage and explorative analysis, not a comprehensive economic evaluation. The use of a CCA to identify potential costs and consequences of the intervention provided a comprehensive overview of the potential impact of VEM. This type of analysis provides an itemised account of the intervention's impact for decision makers to then appraise the components relevant to their perspective. Presenting costs by perspective will facilitate the

assessment of any shift in costs and allow decision makers to make their own judgements. The CCA also enabled resource use items associated with implementation strategies relevant to VEM such as educational sessions (as highlighted in Chapter 5) to be identified. Resource use items, although uncosted, could be used in future economic evaluations of implementation strategies.

When using the primary outcome, independence, the results of the CEA showed that VEM is potentially cost-effective from both healthcare and societal perspectives. Very early mobilisation may result in a faster and/or enhanced recovery therefore facilitating the return to work and/or minimising the loss of productivity. As in the CCA, an ICER was calculated from both healthcare and societal perspectives. A resource intensive intervention delivered in the acute stages after stroke may not be cost-effective from the perspective of the healthcare provider but by minimising loss of productivity may actually be cost-effective from a societal perspective.

The costs relating to informal care may be higher in the VEM group than the SC group. Very early mobilisation has been associated with an earlier and an increased chance of discharge home which could shift care from the healthcare provider to informal carers. This is an important issue in stroke rehabilitation considering the increasing number of stroke patients being discharged directly home. The CEA outcomes were sensitive to the method of costing informal care (as shown in Table 6-5). This finding is likely to be the result of small patient numbers and is not surprising considering the actual number of patients in the SC group who received input from informal carers was higher than in the VEM group (43.8% versus 25.0%).

Strengths and limitations

The main limitation of the systematic review is that multiple definitions and different forms of stroke rehabilitation exist and this may have resulted in studies not being identified by the search strategy. Existing guidance for the systematic review of complex interventions[244] were incorporated and a scoping exercise to encompass relevant subject headings to inform the search strategy

was conducted. Hand searching was also included to increase the sensitivity of the search.

A CCA does not explicitly compare the costs of an intervention with its outcome therefore has been considered not to be an economic evaluation in the strictest sense.[245] It does, however, provide a comprehensive and itemised account of the intervention's impact for decision makers to then appraise the components relevant to their perspective and to identify the most appropriate outcome for use in a future trial. Furthermore, a CCA simply presents all cost and effectiveness outcomes separately, it can include quality of life and health utility outcomes. Therefore, an ICER could still be calculated and compared across different interventions, allowing cost-effectiveness threshold based decisions to be made. The CCA also has appeal for the clinician. It allows for a collaborative approach to decision making, involving clinicians and incorporating factors relevant to routine clinical decision making. This approach also provides a transparent and easy to interpret framework for the clinician.

The planned use of a CEA as well as CUA provided the opportunity to synthesis the cost and effect data. As demonstrated here, presenting an ICER for the primary outcome measure and a secondary health outcome such as the reduction of immobility-related complications ensures that all available evidence is synthesised and presented appropriately.

There are a few limitations with the QALY estimates used in this economic evaluation. Firstly, the calculation of QALYs was limited to the duration of AVERT phase II which required the assumption that there is no lifelong effect of VEM. This analysis was not intended to be a comprehensive analysis, but to provide some indication of the economic impact of VEM. Therefore, future analysis should include formal modelling techniques so as to determine the longer term effect of VEM on length and quality of life. Secondly, within trial QALYs were calculated based on HRQoL data collected at three months and 12 months and this data may not be equivalent to the first three months post-stroke (the time horizon for this CEA).

The sensitivity analysis conducted only varied one factor at a time which may

underestimate the uncertainty as the components of an evaluation do not vary in isolation, however varying two or more factors at a time makes results difficult to interpret.[246] Probabilistic sensitivity analysis is a technique used to provide a level of confidence in the results to the decision maker. Each parameter in the model (for example the probability of independence) is assigned a distribution and using computer software a large number of simulations are run. The results of each of these simulations are recorded and used to present the variation in results. Undertaking probabilistic sensitivity analysis was outwith the scope of this exploratory economic evaluation, however incorporating probabilistic sensitivity analysis would strengthen and highlight areas of uncertainty for future trials.

Recommendations for economic evaluation of stroke rehabilitation

The findings from the systematic review and the economic evaluation together support the development of specific guidelines for conducting economic evaluations of stroke rehabilitation using the generic Drummond et al checklist as the basis for these recommendations. Davis et al[247] have provided guidelines in a similar way for conducting and reporting economic evaluation for fall prevention strategies. This could be used to guide the development of similar guidelines specific to stroke rehabilitation. Such recommendations may include the following:

- Conduct of an economic evaluation alongside a clinical trial to ensure an individual patient data approach to costing data. Details about the implementation of the rehabilitation intervention can then be measured and recorded so that reliable costs can be calculated. Details about the staff member(s) involved in delivering each episode of the intervention and the length of time (dose) of each episode of intervention are examples of resource use that could be collected for rehabilitation-based interventions.

- As there are challenges associated with measuring and valuing all costs and consequences within a single evaluation, an attempt should be made to primarily identify these, as illustrated here, using a cost-consequence

analysis. Other data sources should be used to estimate the value of the costs and consequences where they cannot be measured within the single study.

- The use of multiple ICERs using justifiable secondary clinical outcomes may be appropriate.

Multi-criteria decision analysis for complex interventions

While cost-effectiveness is the key consideration, it is acknowledged that other factors are relevant and are already being taken into account by policy makers. With respect to NICE, these factors have been explicitly stated and include severity of the underlying illness and end of life treatments. The development of multi-criteria decision analysis (MCDA) has the potential to add transparency to the decision making process.[248] Multi-criteria decision making has been defined as "a set of methods and approaches to aid decision making, where decisions are based on more than one criterion, which make explicit the impact on the decision of all the criteria applied and the relative importance attached to them." [249]

There is little known about the weight that is attached to these factors and any others that may come under the judgement bracket. Also, the trade-offs that are made between the cost per QALY and these other factors is not explicit. The MCDA frameworks offers the decision making process a more reliable (different committees provide the same decision) and transparent approach, by rating decision makers preferences for an intervention with respect to these extra criteria such as the quality of evidence, disease impact and ethics.[250] Some MCDA tools involve sophisticated mathematical algorithms to suggest appropriate choices while others aim to structure the process. In the context of complex interventions there is an extra emphasis on describing the intervention and the comparator(s) used in studies in enough detail to allow decision makers, clinicians and researchers to relate these to their own local area. Whether the amount of information provided in the studies included in this systematic review would allow a valid assessment of local applicability is debatable. Thus, 'generalisability' is an example criterion that may be of particular relevance for inclusion in a MCDM framework for complex interventions (Table 6-7).

Table 6-7 Example criteria for multiple-criteria decision making

Criterion	Definition(s)*	Prompt(s) for decision makers**
Generalisabilty	"the extent to which the results of a study, as they apply to a particular patient population and/or a specific context, hold true for another population and/or in a different context."[251]	• Do the results apply to the populations and settings under question?
Implementability	"how well the program is conducted during a trial period"[41]	• What are the barriers and facilitators to implementing the intervention? • What are the costs of implementing the intervention and implementation strategies beyond the trial?
Coherence	"defining the components of a practice, and its differences from other – already established"[252]	• Are the components of the intervention defined? • Is the intervention as a whole readily distinguishable from that of usual care?
Sustainability	"whether the program is maintained over time"[41]	• What is the best decision for longer-term investment i.e. invest in the new treatment or invest in better implementation of available interventions?

* Literature based definitions

** Informed by qualitative findings in Chapter 5

This could easily be viewed as adding to an already considerable number of factors. Alternatively, it could be viewed as a tool to facilitate decision making, not as a tick box exercise. It is important that researchers are aware of the supplementary information that may need to be collected to address these 'prompts' (as outlined in Table 6-7) to inform decision makers. Also, the way in which this information is presented to decision makers to ensure decisions can be made in the allocated time and without being seeing to remove judgements. For example, a process evaluation would elicit information about the barriers and facilitators of the intervention, however, once this information is made available, the challenge may be how best to present this qualitative research to decision makers in an easily interpretable and cohesive manner so as not to delay the decision making process. One suggestion here is for the use of an existing qualitative framework, NPT (as described in Chapter 5), which has been specially designed to assess the implementation of complex interventions. The attractive feature of this framework is that it translates qualitative findings under purposefully developed and defined constructs in a user-friendly way.

6.5 Conclusion

This Chapter includes research that addresses the evaluation stage of the Medical Research Council complex intervention framework. An evidence synthesis approach was used to model the economic impact of very early mobilisation (VEM). The findings from the individual patient data meta-analysis (Chapter 4), the qualitative study (Chapter 5) and the systematic review (Chapter 6) were used. The findings from the systematic review have highlighted the importance of adopting a wider cost and benefit perspective and that a single generic outcome measure has limited used in the economic evaluation of complex interventions such as stroke rehabilitation. The economic evaluation conducted using existing data showed that VEM is potentially cost-effective from a societal perspective. However, the sample size used to model the impact of VEM was too small for any definitive conclusions to be drawn from this analysis. The evaluation did, however, show the value of conducting a cost-consequence analysis to identify the possible costs and consequences pertaining to the intervention and conducting cost-effectiveness analyses alongside a cost-utility analysis for interventions with wide-reaching effects. This Chapter has highlighted the need to evaluate the cost-effectiveness of implementation strategies and suggested the development of multi-criteria decision frameworks in complex intervention research.

7 Conclusions

This Chapter summarises and concludes on the results presented in Chapter 2 to Chapter 6. This thesis is a series of qualitative and quantatative studies which, by converging research findings, contributes to the evidence-base of one of the proposed most important aspects of stroke unit care. New and novel quantitative and qualitative data were generated whilst making use of the best available evidence in order to address the research questions. Whilst, this thesis did not set out to confirm the clinical effectiveness of VEM, it does substantiate the current evidence-base for VEM in terms of favourable outcome and supports the need for AVERT phase III. This thesis has provided vital information required for the early stage of implementation and which can be used to inform the next stages of implementation.

Overall, the main advantage of conducting this extensive body of research has been the opportunity to use a combination of methods to allow the linking, merging and triangulation of data both between and within the studies. Linking data between the studies, for example using the information about predictable variations in outcome to inform the design of the observational study, has illustrated a systematic approach to developing and using new evidence. Merging data within studies, for example the accelerometer data and BMT data, provided a more comprehensive dataset about activity levels and environmental factors had the datasets been analysed seperately. Triangulating data between studies, for example the observational data and the qualitative data, identified important tensions and incongruences in clinical practice. Other advantages included the generation of novel and rich data and the chance to cut across different disciplines. However, the main drawback of conducting this research has been the use of resource intensive methods, such as the systematic reviews of complex interventions and the conduct of the BMT.

This Chapter also details the literature that has emerged recently with regards to early mobilisation in stroke, the next stages of implementation if VEM is shown to be effective and finally some suggestions for quality measures that may be appropriate to monitor VEM in the future. Finally, the Chapter suggests specific implementation activities that could be conducted to study the

implementation of a complex intervention and highlights important issues raised in this thesis that could be applied more generally to implementation science.

7.1 Summary of key findings

7.1.1 Chapter 2

Baseline factors predictive of mobility after stroke

There is a dearth of studies that aimed to identify factors predictive of or associated with mobility within 30 days post-stroke in comparison to the number of studies investigating the predictors of function or disability in the longer-term. The systematic review identified baseline factors that may have value in predicting mobility, more specifically independent walking, within 30 days post-stroke. The systematic review showed that age, the severity of paresis, reduced leg power, presence of hemianopia, size of brain lesion and type of stroke were all predictive of or associated with walking within 30 days post-stroke. The potential overlap in meaning between the two factors - severity of paresis and reduced leg power is noted, however, due to the limited reporting of the definitions and methods to measure these factors it was considered appropriate to present these two factors separately. All of the factors identified in this review have been previously reported in individual studies investigating predictive factors of function or disability. The presence of hemianopia and the size of brain lesion appear to be less researched and most controversial.[253] The size of brain lesion is not routinely available in clinical documentation and may be one reason for this factor not being included in predictive studies. The findings of this review are based on a limited number of studies. On assessing the quality of these studies using best practice principles for conducting predictive research revealed limitations. In an attempt to overcome these methodological shortcomings two new predictive models were subsequently developed using registry data; Model 1 used the factors identified by the systematic review and Model 2 used the factors identified by clinical opinion and univariate analysis. The factors identified by the systematic review were shown to be predictors of walking and constituted Model 1. In addition, to age and stroke type, Model 2 also included living arrangements on admission, baseline

level of stroke severity, level of disability and level of ADL as predictors.

The immediate application of these findings was to inform the factors to be collected at baseline in the observational study that may be important when investigating patient activity levels. The factors were used to adjust for patient case-mix in the analysis investigating the association between activity in the acute stages after stroke and function at three and six months. There is an obvious limitation in this planned for systematic approach. Chapter 3 aimed to investigate the association between activity in the acute stages after stroke and function at three and six months, not mobility.

Whilst predictive models can reveal differences in the recovery profiles of subgroups of patients these do not take individual patient responses to rehabilitation interventions into account. The level of stroke severity was shown to be the strongest predictor in the final model. Chapter 4 provided the opportunity to explore (with caution) responses to a rehabilitation intervention in patients with different groups of severity.

7.1.2 Chapter 3

Baseline levels of activity in acute stroke patients

The most obvious finding to emerge in Chapter 3 was to confirm the low levels of upright activity in acute stroke patients; however, the prolonged periods of time spent in sedentary events may be more cause for concern. Chapter 3 has provided a precise estimate of the time spent upright and time spent sedentary in a sample of acute stroke patients from three Scottish hospitals using accelerometry. Patients spent the majority of time sitting in a chair at the bedside. The majority of total upright time was the result of short episodes of less than 10 minutes. The opposite pattern was observed for sedentary behaviour whereby the majority of total sedentary time was accumulated by prolonged episodes of greater than 60 minutes sedentary behaviour. Nearly all sedentary time for patients with moderate/severe stroke was accumulated in this way.

This baseline measure of activity could be used to inform the design and implementation of future activity-based rehabilitation interventions in acute stroke care. Measuring patterns of activity is important in order to develop interventions. It can assist in understanding relationships between activity and routine ward processes and inform delivery of the day-to-day implementation of such activities such as the time of day the intervention should be delivered. Accelerometer-based measures are important process indicators or outcome measures that could be included in future observational and interventional studies.

7.1.3 Chapter 4

Clinical impact of very early mobilisation

Chapter 4 provided a more precise estimate of effect for VEM in relation to independence at three months post-stroke than that previously reported. In both AVERT phase II and VERITAS, VEM patients received earlier and more frequent mobility practice than that routinely provided. The treatment effect on the primary outcome in both trials was in favour of VEM suggesting, along with evidence for the use of a fixed effect model, that the individual studies were estimating the same treatment effect. Very early mobilisation had a favourable impact on the secondary outcomes. This varied by effect size and the level of significance. The relevance of VEM in reducing immobility-related complications at one week (significant reduction) and at three months (non-significant reduction) after stroke is supported by the findings in Chapter 4. Levels of mobility and levels of independence in ADL were significantly better for VEM patients than SC patients at three months. The only outcome that VEM had little effect on was the chances of death. Some may consider this unsurprising as reducing the odds of death may not be seen as an obvious outcome for a rehabilitation intervention. The primary outcome used in the ongoing AVERT phase III is death and disability with mobility as a secondary outcome. This choice of primary outcome allows for the findings of this trial to be compared with other acute stroke interventions and to be interpreted in the context of the estimated effect size of ASUs.

Very early mobilisation had the largest and most significant effect on mobility with a patient undergoing VEM seven times more likely to have non-impaired mobility than a SC patient. This analysis indicates that VEM has the potential to influence the early recovery of general mobility and ability to walk. This is important considering the ability to walk is a determinant of longer term functional recovery. Both studies are limited by small sample sizes supporting the need for larger trials to determine the effectiveness of VEM. Therefore, at this point in time it would be inappropriate to make recommendations on the use of VEM in stroke. Early mobilisation features in a number of guidelines throughout the world, but specific recommendations cannot be made until robust evidence to guide the practice has emerged from the AVERT phase III, after which time there will be greater clarity about the harms and benefits of VEM.

7.1.4 Chapter 5

Barriers, facilitators and beliefs of very early mobilisation

Chapter 5 has provided data on current stroke processes, pre-existing context and the factors that may influence the future implementation of VEM. It has also provided rich data about the complex array of individual, intervention specific and environmental elements that influence change. Staff questioned the workability and integration of VEM into routine practice if shown to be effective. The AVERT phase III is multinational and guidelines are frequently being set by international committees. Therefore, Chapter 5 supports the need for a global statement about the implementation of VEM. Suggestions for the next stages of implementation are covered in Section 7.3.2.

The findings from the qualitative study were interpreted in parallel with the researcher observations conducted in Chapter 3. These researcher observations could be viewed as a context evaluation as it studied "naturally occurring events and influences in the setting or environment of the intervention that might act to contribute to or impede intervention success".[37] There was congruence between what was observed and what was said. Incongruence was also identified. These are essential observations to highlight when considering

behavioural change. Capturing information about the pre-existing context is important to assess the compatibility of the intervention with the local context. It is helpful in generating hypotheses about the hospitals that may have difficulty in implementing the intervention. For example, it could be hypothesised that the uptake and sustainability of VEM may be unstable in sites without a history of successful change or strong collaboration between therapists and nurses. The implementation of VEM could be seen to have an auxiliary role in forging new collaborations between departments and by strengthening relationships between groups of ward staff with increased opportunity for interaction, shared working and patient goal-setting.

Chapter 5 forms the basis and justification for a multicentre qualitative study to further explore and validate the identified barriers and facilitators in other countries. The generalisability of these factors could be assessed and the potential requirement for country specific implementation strategies could be addressed. This is imperative if the findings of the trial are going to reach and inform practices across the globe. Furthermore, the contextual factors identified in Chapter 5 may not be transferable to hospitals outside of Scotland, therefore there is a need for local study which will contribute to the building of theory around the process of implementation. All staff involved in this study were aware of VEM, either currently involved in delivering the intervention or were aware of the trial via colleagues or conference attendance. It would be of interest to capture the views from staff working in countries that are not involved in AVERT phase III in an attempt to minimise this contamination. Different issues may be raised for the implementation of VEM at these 'clean-sheet' hospitals. Further evaluations should involve experts in behavioural change and adopt a theory-driven approach to ensure that VEM has and is associated with a clear and cost-effective implementation strategy.

A quantitative process evaluation that aimed to monitor the activity levels of trial patients using accelerometry would allow implementation fidelity to be assessed objectively i.e. the degree to which the intervention is actually implemented. Data about the actual single dose duration, frequency and schedule of activity undertaken by VEM patients would have allowed the development of reliable and objective indicators. For example, actual time

spent in upright activity would be measured and distinguished from time spent with the patient (currently recorded in AVERT phase III). Such objective indicators could then be used to assess the implementation of VEM in real-life. Until recently, the process data currently collected in AVERT phase III does not provide a continuous measure of activity or information about self-mobilisation (outside that recorded by trial staff) that may be a consequence to the intervention. A substudy (AVERTcog)[254] of AVERT phase III is now underway which monitors the activity level of AVERT phase III trial patients using an AC (SenseWear). Using the data from AVERTcog, the pattern of activity between the SC and VEM groups could be compared and expected activity profiles for patients receiving VEM derived. Whether SC and VEM patients respond in a similar manner to monitoring, as too with staff delivering the intervention to either group, is an interesting area and should be explored. The therapy dose delivered to patients recruited to AVERTcog with those recruited to only AVERT phase III could be compared. The findings of AVERTcog may allow the investigators to state, that it supports, along with routine monitoring of intervention implementation (as discussed in Chapter 4) that the intervention was delivered as intended. Otherwise, if the findings are not favourable it could be speculated that this was due to implementation failure as opposed to the inherent failure of the intervention.

7.1.5 Chapter 6

Economic impact of very early mobilisation

The systematic review showed that most of the economic evaluations compared conventional rehabilitation with an early supported discharge team either using a CMA or CCA type approach. A CUA, which uses QALYs to infer health benefits, is the economic analysis preferred by decision makers such as NICE. When the findings from this review were considered within this decision making context, the use of such a single outcome could be viewed as inappropriate and limited in representing the multiple health benefits of stroke rehabilitation. Indeed, VEM did not appear to affect HRQoL and was not associated with a gain in QALYs. It may well be that there is no theoretical basis to support the notion that VEM affects quality of life. It has been stated elsewhere that interventions targeted

at older people are unlikely to generate any additional QALYs.[255] In any case using a single outcome offers little scope to consider the wider and non-health effects of stroke rehabilitation such as productivity costs, patient education and the impact on carers. The limitations of the use of QALYs have been raised elsewhere and the findings from this review support a move away from traditional decision making based purely on cost-effectiveness, towards MCDM for stroke rehabilitation, where a broader perspective is adopted and a range of criteria are assessed by policy makers.

The ICERs associated with the effectiveness outcomes suggest that VEM is potentially cost-effective when considering the NICE threshold of £20,000-£30,000. For example, the ICER associated with VEM in comparison to SC was approximately an additional £200 per additional patient achieving independence. These estimates are based on a very small number of patients and the cost-effectiveness of VEM will be better estimated using the findings from the AVERT phase III study. The findings from the systematic review and the economic evaluation together support the development of comprehensive guidelines for conducting CEA in stroke rehabilitation using the generic Drummond et al checklist as the basis for these recommendations.[206] Davis et al have provided guidelines in a similar way for conducting and reporting economic evaluation for fall prevention strategies.[247] This should be used to guide the development of similar guidelines specific to stroke rehabilitation.

7.2 Critique of methods

Overall, a systematic approach, guided by the MRC complex intervention framework has been used. A combination of methods was of value to generate new data and analyse existing data in order to address the aim of this research. These included evidence synthesis, observational and qualitative research methods. Areas of health research, including health services research and health technology assessment have emerged as a result of political and economic pressures. These research fields aim to bring together clinicians, social scientists and statisticians to clinically and economically evaluate interventions. This thesis provides an example of health service research as it stands today.

Evidence synthesis approach

The systematic reviews conducted in this thesis have been carried out according to the principles set out in the Preferred Reporting Items for Systematic Review and Meta-Analysis guidance. Assessing the methodological quality of the included studies in the systematic reviews (Chapter 2 and Chapter 6) allowed recommendations to be made, some of which were subsequently utilised in the development of the predictive models and the economic evaluation. The predictive modelling in Chapter 2 used a systematic method to selecting the factors to develop the model and tested the performance of the models. The findings from the review highlighted these as common methodological shortcomings. The final development of the predictive models was not without limitations, for example: the selection of factors was based on the opinions of only two clinical experts. A Delphi-method where a panel of experts are used to provide consensus would provide a more robust approach. Additionally, the model was not externally validated. The data set generated for Chapter 3 would not have provided sufficient statistical power to validate the predictive models. Similarly, the economic evaluation in Chapter 6 makes use of the recommendations from the review by conducting a CEA to synthesis the cost and effect data.

The IPD MA conducted in Chapter 4 should be viewed as an illustration of applying this method to complex intervention research. Undertaking a meta-analysis can increase statistical power, and especially with regards to complex interventions, IPD MA offers advantages over meta-analysis of aggregate data. Individual patient data meta-analysis is deemed time consuming, and although in this IPD MA there were only two studies, the greatest amount of time was invested in data manipulation to re-code and re-format data to ensure it could be combined. Future protocols for IPD MA should provide guidance to trialists about the expected format of the data to be included in the meta-analysis. One of the main advantages in conducting an IPD MA is the opportunity to study potential confounders and effect modifiers for future regression analysis. Again, numbers were small in each of the pre-determined subgroups so no firm conclusions can be drawn. This IPD MA should, therefore, be viewed as a hypothesis generating exercise, particularly for the groups of patients that may

respond differently to rehabilitation interventions. It could also support the need for and inform subgroup analysis of larger future trials and IPD MA investigating intensive therapy regimes. Combining individual patient data in this way has emphasised the importance of sharing protocols and agreeing outcomes to reduce variations between trials and ensure comparability of trials of complex intervention.

An evidence synthesis approach was used to estimate the economic impact of VEM. The findings from Chapter 4 (IPD MA), Chapter 5 (qualitative study) and Chapter 6 (systematic review) were used. The analyses conducted illustrated the value of a CCA to identify potential cost and consequences of the intervention and to inform the outcomes for use in a CEA. The sample size of the study was small, yet, satisfies the recommendations provided in the MRC framework which encourages the use of small scale analysis in the early evaluation of complex interventions.

Predictive modelling

Generally, such predictive models have use in both research and clinical practice. For the purposes of research it is important to be able to classify patients into balanced prognosis groups.[59] Stratifying patients based on predictive outcome has been used in comparative audits to evaluate the efficacy of care in different hospitals.[256] Forty percent of stroke patients have been said to need active rehabilitation.[257] Therefore, having accurate estimates of the likelihood and timing of mobility recovery would help to determine the appropriate placement and timing of rehabilitative efforts in different groups of patients who have this activity limitation. This need to inform the efficient allocation of resources has supported the development of such models. Predicting patient's mobility status post-stroke, such as the likelihood of ambulation, is of great clinical relevance, providing vital information to HCPs, patients and their families.[57 77 258]

The application of predictive models relies on having strong evidence that the recovery profile of patients can be robustly determined by such predictions. Furthermore, these models must be used routinely in clinical practice. To

increase the uptake of predictive models it is important to improve a clinician's confidence in the tools and to confirm that the model predictions compare favourably with clinician predictions. The current use or avoidance of prediction tools in clinical practice needs to be addressed. It is important that before a tool is used clinically it is evaluated in a RCT to compare outcomes for patients managed using the model with patients who were not managed with the model. Evaluating the cost-effectiveness of predictive models are not usually conducted. This would allow the full impact of predictive tools to be assessed in terms of the cost implications and consequences for the patient and family where accurate or inaccurate information is provided.

Technology used in the observational study

Novel and established methods for monitoring activity were used in Chapter 3, explored and compared. The method used to integrate the AC data with the BMT data to provide objective data on location and stroke processes offers a model for analysis of similar data sets. Chapter 3 highlights the need for further investigations into the use of ACs in patients with altered biomechanics and reduced heel strike. Despite synchronising the AC data with the observational data, no firm conclusions can be drawn about the accuracy of the *activ*PAL™ in detecting stepping as this study was not a validity study. A validation study conducted in an ASU with patients stratified according to existing gait classifications into homogenous groups[259] needs to be conducted. The *activ*PAL™ does not distinguish lying or sitting therefore the establishment of algorithms to detect sitting from lying or the use of the *activ*PAL™ system as a two-sensor unit are areas of further work. The *activ*PAL™ does not have a start/stop button so does pose challenges for use in an acute hospital environment in the absence of a study co-ordinator.

Further technological advancements could be enhanced with greater collaboration between manufacturers and researchers. Guidance for the use of ACs in stroke i.e. choice of device and decisions around the analysis of data such as how to manage missing data are required. The potential for accelerometry to provide feedback to patients and clinicians on performance should be investigated in the future. Behavioural mapping makes the findings directly

comparable with that of other completed and ongoing mapping studies. Discussion regarding a future IPD MA using multinational BMT data has been initiated (personal communication, 2012). Any differences in activity levels between countries could be identified and explained using rich comparable data.

Qualitative methods

The findings are based on a relevant sample of HCPs and provides multiple and diverse perspectives. However, no nursing assistants participated in the study and considering they deliver a large proportion of patient care and are involved in the day-to-day mobilisation of patients, this is a shortcoming. One of the strengths of this analysis was to be able to triangulate two new sets of data (the observational data and the qualitative data). This provided an opportunity to highlight discrepancies between what staff believe they do and what they actually do.

Chapter 5 is limited in providing details on the relative importance of barriers. This may have particular relevance in the area of implementation science whereby the relative importance of each of the barriers and facilitators may be required to guide investment decisions around implementation strategies. The use of DCEs to investigate preferences was discussed as a method to overcome this limitation.

7.3 The future study of very early mobilisation

7.3.1 Emerging literature on early mobilisation

The IPD MA (Chapter 4) was informed by a Cochrane review based on a search conducted in April 2008. Due to the growing interest in VEM and since the release of this Cochrane review several studies have been published investigating the effects of early mobilisation. Although, the more recent studies identified do not meet the criteria of the Cochrane review (due to the definition of VEM) it is still important to be aware of the evidence base of early mobilisation and current mobilisation practices across the globe. Most recently, Sundseth et al (2012) conducted a RCT to investigate the effect mobilisation

within 24 hours after admission (versus mobilisation after 48 hours) had on mortality or disability three months post-stroke.[260] This study found that patients in the control group had more favourable outcomes. This finding was not statistically significant before or after adjustment and the sample size was small (n = 56). Canavero et al (2012) used patient admission data (n = 9787) to examine the impact of early mobilisation (within 48 hours) on within hospital mortality and medical/neurological complications.[261] Early mobilisation was significantly associated with better survival at discharge, yet was associated with a significantly higher chance of in-hospital cardiovascular complications and falls. The authors concluded that there would need to be attention to monitoring during this procedure. A study conducted in Japan by Matui et al (2010) explored the association between very early rehabilitation and outcome for patients using a retrospective cohort study design. Very early rehabilitation commenced within three days of stroke rehabilitation was significantly associated with less disability at discharge.[262]

7.3.2 Future implementation of very early mobilisation

The AVERT phase III trial, being sufficiently powered and pragmatically designed, is well placed to provide reliable evidence about the effectiveness of VEM. If shown to be effective, the trialists can make recommendations about the 'form' of VEM and the real-life implementation can begin. If shown to be no more effective than SC, the trialists can still make recommendations about mobilisation practices based on SC.

At face value, HCPs believed that VEM is similar to the early mobilisation practices that they currently practice. Therefore, the act of implementation in this case is likely to be even more challenging in that it will involve the replacement of an intervention with another that has similar properties. Whilst implementation usually involves the end or changing of current behaviours and the introduction of new behaviours, changing current practice is likely to prove most challenging in the future implementation of VEM.

Interventions shown to be effective, but are never implemented provide no benefit to patients. This thesis has provided vital information required for the

early stage of implementation as described in Grol and Wensing's (2006) 'Model for Effective Implementation' (Chapter 1). Current practice and relevant practice issues (problems or best practice) have been identified. Recommendations for developing evidence-based implementation strategies have been provided. This early stage implementation research supports the need for a clear implementation plan for VEM which may require the input of a behavioural change scientist to work with staff to alleviate concerns towards change (Chapter 5, Section 5.3.17) and design appropriate implementation strategies (Chapter 5, Section 5.3.11).

The next stage of implementation should further investigate current practice and the context where change will take place at other hospitals outside Scotland. It is also important that the individuals responsible for implementing a complex intervention know the context in which the intervention was evaluated. This provides the opportunity to consider any differences between the context of evaluation and the context for implementation.

Operational change objectives need to be set and the implementation strategies outlined in Chapter 5 should be further developed and tested. Multidisciplinary communication in the form of brief daily morning meetings was identified as a facilitator for VEM. Therefore, an example of an operational change objective could be to embed such meetings into daily ward practice for those sites that do not currently employ these meetings. The final stage of implementation would be to put the implementation plan i.e. who does what, and when into action and to conduct a comprehensive evaluation of process and outcome.

7.3.3 Quality measures for very early mobilisation

Measures will need to be developed and put in place to monitor any future implementation, only then can the true success of VEM be assessed. The NICE quality statement introduced in Chapter 3 regarding the amount of therapy time that should be provided to acute stroke patients is underpinned by a set of quality measures to assess the implementation of this statement. For example, the quality measure for 'structure', (as introduced in Chapter 1), is the evidence that local arrangements are in place for the provision of a minimum of 45

minutes of each active therapy for a minimum of five days a week. Similarly, quality measures to assess the success of implementation of VEM should be defined. Quality measures could aim to address the following questions:

- What education is available to new or existing staff about very early mobilisation?
- Is very early mobilisation discussed and recorded during multidisciplinary meetings?
- Do any members of staff have implementing the policy of very early mobilisation embedded within their job description?
- Has the way in which mobilisation provided, changed?
- Have any new systems been introduced as a result of very early mobilisation i.e. a referral system, use of visual mobilisation charts by the patient's bedside, ward timetables for patients?
- Is the very early mobilisation policy integrated into organisations or local agency strategy documents?
- Is or was there any funding allocated for the implementation and sustainability of very early mobilisation and if so what is the source of this funding?

Very early mobilisation is multidimensional and consists of various variable components i.e. timing, amount, frequency and type of mobilisation. Therefore, identifying and defining valid quality measures may be challenging or even inappropriate for an intervention such as VEM.

7.4 The future study of implementing complex interventions

7.4.1 Specific implementation activities

As Chapter 1 underlined there has been more attention given to the implementation of complex interventions in the most recent MRC guidance

document. Researchers are asked to think about the impact of results in terms of whether they are accessible to decision makers and recommendations are detailed and explicit. Considering implementation early on in the research of complex interventions is essential to assess how easily the intervention can be implemented into real-life. An intervention may have little chance of real-life implementation therefore should be discarded on these grounds as opposed to embarking on a full scale and costly evaluation investing finite resources.[263] Attracting funding for these smaller scale developmental activities is more challenging.

It is recommended that implementation related-activities are extended to consider the following:

- The use of process data monitoring committees as well as outcome data monitoring committees during the main evaluation stage
- Integrating the findings of process evaluations whilst the intervention is under evaluation. This takes time especially for investigators to consider reports and make decisions whether or not to act upon these.[264]
- Further methods to study context and the wider use of existing theoretical frameworks such as the normalisation process theory specifically developed for studying the implementation of complex interventions
- Complexity of the intervention lies just as much in context as in the components of the intervention. More time needs to be invested into the study of context. The use of in-house ethnographers may have more to offer than developing sophisticated causal models to disentangle the infamous "black box".
- The longevity of implementation strategies should be evaluated to assess how effective they are in sustaining the intervention beyond the dissemination, adoption and implementation stages

Furthermore, the impact that the research itself has on the intervention is an interesting area. The media coverage, involvement of opinion leaders and

ground-level staff in clinical trials may impact on implementation both during the trial phase and later into real-life, by shaping HCPs and the public's view of the intervention. Recruitment to large trials of complex interventions take years and changes in the clinical, research, economic and political landscapes may impact on the design of the study and intervention and the findings (practice creep).

7.4.2 Recommendations for implementation science

This thesis does raise some important issues relating to theory, research, policy and long-term monitoring that can be applied more generally to implementation science.

Models and theories for use in implementation research

There appears to be a lack of simple yet theoretically driven approaches to understanding HCPs' beliefs and organisational change. This limits the ability to assess the applicability of implementation strategies in different circumstances. Models and theories that aim to explain change and how it can be influenced are likely to be of most benefit in implementation research. There are a number of models and theories that exist which explain implementation and behavioural change and include the theory of planned behaviour, the diffusion of innovations and the PRECEED/PROCEED Model. [265-267].

The theory of planned behaviour has considerable evidence around its use and provides a list of behavioural influences known to affect the use of guidelines. It has been used to explain associations between beliefs, attitudes, social influences (social norms), and perceived abilities to perform the behaviour.[265] The diffusion of innovations aims to explain how interventions are taken up in a population and differs to other theories of changes in that it focuses more on how the intervention evolves to meet the demands of the population and not how people change.[266] This theory also classifies people into groups ranging from the 'innovators' (those that are motivated by new ideas) to the 'Laggards' (those that resist change). The PRECEDE/PROCEED model can be used to plan and explain change in patient care with the initial stages of the model aimed at

identifying the factors (those that are predisposing, enabling and reinforcing) that influence change.[267] The later stages of the model focus on developing the best approach and incorporate an evaluation of process, impact and effect.

The 'Model for Effective Implementation' referred to in this thesis focuses more on planning change and takes the perspective of both the 'implementer' (the person/organisation instigating change) and the 'target' group (the team/individual that needs to go through the change).[36] It offers an attractive stepwise and pragmatic approach with the initial stages involving the identification of current practice then describing operational change objectives and finally developing implementation strategies.

Clinical considerations and research methods

This thesis has highlighted the importance of treatment differentiation at a clinical and research level, conducting an evaluation of pre-existing context and collaboration between the developers, the providers and the intended population of the intervention. Healthcare professionals have high regard for clinical judgement so more guidance is required about how to develop and implement protocols/guidelines without compromising clinical judgement. Due to the patient dependent nature of complex interventions this is an important balance to strike. Previous studies in the area of implementation science have provided an array of barriers and facilitators [268-270] but most of these, as with the qualitative study (Chapter 5) are limited to providing quantitative detail around the relative importance of barriers. The value of applying DCE methodology in implementation science should be explored to provide quantitative data in this complex study of barriers and facilitators.

Whilst conducting this research and engaging with experts in complex intervention research (personal communication, 2010) there also appeared to be a lack of evidence-based approaches stated in the literature which could be used in the dissemination stage of implementation. Intervention dissemination groups should be formed to conduct priming activities to motivate the target audience to being open to future change with efforts to ensure the intervention has a marketable 'buy-in'. Guidance of the timing of such activities is needed.

Policy

To ensure that findings are translated into policy, it is important that they are made available using methods that are in an interpretable format and convincing to decision makers. Some of the recommendations made in this thesis have direct implications for policy. In Chapter 6, the suggestion is for the use of NPT to translate findings from qualitative research (such as barriers to implementation) into a format policy makers are accustomed to. Additionally, Chapter 6 highlighted the development of multi-criteria decision analysis where a broader range of criteria relevant to complex interventions be assessed by policy makers. Such frameworks would allow the consideration of factors other than just cost-effectiveness when considering whether or not to adopt a certain intervention. This is important when considering the wide-reaching impact of complex interventions.

Long-term monitoring

Experimental studies rarely provide comprehensive information on the longer-term effectiveness and generalisability of the intervention. Trials are not usually powered to detect rare adverse events and even adopting a wide inclusion criteria has limitations such as selection bias. Therefore, it is important to monitor the effects of the intervention in the long-term especially considering that effects are likely to be reduced and unanticipated consequences of the intervention may begin to emerge.[29] New ways of routinely embedding long-term surveillance of new interventions was raised by the UK government a few years ago.[271]

> *"We recommend that the Department should seek to introduce a national system for reviewing and tracking the implementation of new devices over a number of years to ensure patient safety and efficacy issues are closely monitored. Currently there is no clear system for determining safety and efficacy beyond the clinical trials and evidence-based model of the Health Technology Assessment (HTA) programme" House of Commons Health Committee, 2005*

This requires re-thinking and investment (is it doubtful that current IT systems are comprehensive enough to support such monitoring) into how the cycle of audit and feedback is currently conducted in healthcare.

7.5 Conclusion

This thesis has adhered to current guidance provided by the Medical Research Council to develop and evaluate VEM. The clinical effectiveness and cost-effectiveness of VEM were investigated revealing that VEM may have the potential to improve patient outcome and be cost-effective. Barriers and facilitators to implementing VEM in routine stroke care were identified. The AVERT phase III trial will provide definitive evidence about the cost-effectiveness taking into account the wider implications of VEM. Only after this, can recommendations be made about the use of VEM in acute stroke care and the real-life implementation and monitoring of VEM commence. This research has provided the support and the foundations for the development of a clear implementation strategy for VEM.

Appendices

Appendix 1 Search strategies for databases (Chapter 2)

Medical Literature Analysis and Retrieval System Online (Medline)

1. Epidemiologic studies/
2. exp case control studies/
3. exp cohort studies/
4. Case control.tw.
5. (cohort adj1 (study or studies)).two.
6. Cohort analy*.tw.
7. (Follow up adj1 (study or studies)).tw.
8. (observational adj (study or studies)).tw.
9. Longitudinal.tw.
10. Retrospective.tw.
11. Cross sectional.tw.
12. Cross-sectional studies/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. exp cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp basal ganglia hemorrhage/ or exp brain ischemia/ or exp brain infarction/ or exp brain stem infarctions/ or exp cerebral infarction/ or exp infarction, anterior cerebral artery/ or exp infarction, middle cerebral artery/ or exp infarction, posterior cerebral artery/ or exp hypoxia-ischemia, brain/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or exp cerebral hemorrhage/ or exp subarachnoid hemorrhage/ or stroke/

15. ((cerebral* or cerebellar or brainstem or vertebrobasilar or stroke) adj5 (infarct* or ischaemi* or ischemi* or thrombo* or emboli* or apoplexy)).tw.
16. hemiplegia/ or exp paresis/
17. (hemipleg* or hemipar* or paresis or paretic).tw.
18. (stroke or poststroke or post-stroke or cva* or cerebral vascular accident* or cerebrovascular accident*).tw.
19. ((cerebral or brain or subarachnoid) adj5 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)).tw.
20. 18 or 19 or 16 or 15 or 17 or 14
21. "Infant"/
22. "Infant, Newborn"/
23. "Child"/
24. "Child, Preschool"/
25. "Infant, Premature, Diseases"/
26. (infan* or child or childhood or children).tw.
27. or/21-26
28. exp locomotion/ or exp walking/ or exp Gait/ or exp Movement/ or exp Motor Skills/ or exp Motor Activity/ or exp mobility limitation/
29. (mobil* or motor* or sit* or stand* or walk* or stair* or ambulant* or ambulat* or gait or step* or balanc* or function* or daily living or disabilit* or physical* or movement or activit* or locomot*).tw.
30. (recover* or outcome* or milestone*).tw.
31. exp "recovery of function"/
32. 28 or 29

33. 30 or 31
34. exp Prognosis/
35. (predict* or prognos*).tw.
36. 35 or 34
37. ((indicat* or determin* or factor*) adj5 (mobil* or motor* or sit* or stand* or walk* or stair* or ambulant* or ambulat* or gait or step* or balanc* or function* or daily living or disabilit* or physical* or movement or activit* or locomot*)).tw.
38. 37 and 36 and 13 and 20
39. 34 and 28 and 13 and 20
40. 38 or 39
41. ((recover* or outcome* or milestone*) adj5 (indicat* or determin* or factor*)).tw.
42. 36 and 13 and 41 and 29 and 20
43. ((predict* or prognos*) adj5 (recover* or outcome* or milestone*)).tw.
44. 13 and 44 and 29 and 20
45. 45 or 42 or 40
46. 45 not 27

Excerpta Medica Database (Embase)

1. Clinical study/
2. case control study/
3. Family study/
4. Longitudinal study/

5. Retrospective study/
6. Prospective study/
7. Randomized controlled trials/
8. 6 not 7
9. Cohort analysis/
10. (Cohort adj (study or studies)).mp.
11. (Case control adj (study or studies)).tw.
12. (follow up adj (study or studies)).tw.
13. (observational adj (study or studies)).tw.
14. (epidemiologic$ adj (study or studies)).tw.
15. (cross sectional adj (study or studies)).tw.
16. or/1-5,8-15
17. exp cerebrovascular disease/ or exp basal ganglia hemorrhage/ or exp brain ischemia/ or exp brain infarction/ or exp brain hematoma/ or exp brain stem infarctions/ or exp brain hemorrhage/ or exp cerebral artery disease/ or exp brain embolism/ or exp subarachnoid hemorrhage/ or exp stroke/
18. ((cerebral* or cerebellar or brainstem or vertebrobasilar or stroke) adj5 (infarct* or ischaemi* or ischemi* or thrombo* or emboli* or apoplexy)).tw.
19. exp hemiplegia/ or exp paresis/
20. (hemipleg* or hemipar* or paresis or paretic).tw.
21. (stroke or poststroke or post-stroke or cva* or cerebral vascular accident* or cerebrovascular accident*).tw.
22. ((cerebral or brain or subarachnoid) adj5 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)).tw.

23. or/17-22

24. exp child/

25. exp infant/

26. (infan* or child or childhood or children).tw.

27. or/24-26

28. exp locomotion/ or exp walking/ or exp Gait/or exp body movement/ or exp patient mobility/ or exp physical mobility/ or exp motor performance/ or exp motor activity/ or exp walking difficulty/

29. (mobil* or motor* or sit* or stand* or walk* or stair* or ambulant* or ambulat* or gait or step* or balanc* or function* or daily living or disabilit* or physical* or movement or activit* or locomot*).tw.

30. (recover* or outcome* or milestone*).tw.

31. 28 or 29

32. exp prognosis/

33. (predict* or prognos*).tw.

34. 32 or 33

35. ((indicat* or determin* or factor*) adj5 (mobil* or motor* or sit* or stand* or walk* or stair* or ambulant* or ambulat* or gait or step* or balanc* or function* or daily living or disabilit* or physical* or movement or activit* or locomot*)).tw

36. 16 and 23 and 35 and 34

37. 16 and 23 and 32 and 28

38. 36 or 37

39. ((recover* or outcome* or milestone*) adj5 (indicat* or determin* or factor*)).tw.

40. 16 and 23 and 34 and 39 and 29

41. ((predict* or prognos*) adj5 (recover* or outcome* or milestone*)).tw

42. 16 and 23 and 41 and 28

43. 16 and 23 and 30 and 34 and 31

44. 38 or 40 or 42 or 43

45. 44 not 27

Allied and alternative medicine database (AMED)

1. exp prospective studies/
2. exp case control studies/
3. exp longitudinal studies/
4. exp cohort studies/
5. exp retrospective studies/
6. (observational adj (study or studies)).tw.
7. (follow up adj (study or studies)).tw.
8. (epidemiologic$ adj (study or studies)).tw.
9. (cross sectional adj (study or studies)).tw.
10. or/1-9
11. exp cerebrovascular disorders/
12. ((cerebral* or cerebellar or brainstem or vertebrobasilar or stroke) adj5 (infarct* or ischaemi* or ischemi* or thrombo* or emboli* or apoplexy)).tw.
13. exp hemiplegia/
14. (hemipleg* or hemipar* or paresis or paretic).tw.

15. (stroke or poststroke or post-stroke or cva* or cerebral vascular accident* or cerebrovascular accident*).tw.

16. ((cerebral or brain or subarachnoid) adj5 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)).tw.

17. or/11-16

18. exp child/

19. exp infant/

20. (infan* or child or childhood or children).tw.

21. or/18-20

22. exp locomotion/ or exp Walking/ or exp Gait/ or exp movement/ or exp Motor activity/ or exp motor skills/

23. (mobil* or motor* or sit* or stand* or walk* or stair* or ambulant* or ambulat* or gait or step* or balanc* or function* or daily living or disabilit* or physical* or movement or activit* or locomot*).tw.

24. (recover* or outcome* or milestone*)

25. 23 or 24

26. exp Prognosis/

27. (predict* or prognos*).tw.

28. 26 or 27

29. ((indicat* or determin* or factor*) adj5 (mobil* or motor* or sit* or stand* or walk* or stair* or ambulant* or ambulat* or gait or step* or balanc* or function* or daily living or disabilit* or physical* or movement or activit* or locomot*)).tw.

30. 10 and 17 and 29 and 28

31. 10 and 17 and 22 and 26

32. 30 or 31

33. ((recover* or outcome* or milestone*) adj5 (indicat* or determin* or factor*)).tw.

34. 10 and 17 and 28 and 23 and 33

35. ((predict* or prognos*) adj5 (recover* or outcome* or milestone*)).tw.

36. 10 and 17 and 35 and 23

37. 10 and 17 and 25 and 28 and 24

38. 32 or 34 or 36 or 37

39. 38 not 21

Cumulative Index to Nursing and Allied Health Literature (CINHAL)

1. ("Prognosis") or (MH "Prognosis+") or (MH "Outcomes (Health Care)")
2. (MH "Stroke") or ("stroke" or "poststroke" or "post-stroke" or "cva*" or "cerebral vascular accident*")
3. (MH "Physical Mobility") or (MH "Motor Activity") or (MH "Physical Activity") or (MH "Functional Status")

Web of Science (WoS)

1. TS=("Physical Mobility" or "Motor Activity" or "Physical Activity" or "Functional Recovery" or "Motor Recovery" or "Physical Disabilit*" or "walk*" or "sit to stand" or "step*")
2. TS=(Prognosis or predict* or prognos*)
3. TS=(stroke or cva or "cerebral vascular" or cerebrovascular)

System for Information on Grey Literature in Europe (SIGLE)

1. (stroke OR poststroke OR "post-stroke" OR cva OR cerebrovasc* OR cerebral* OR intracerebral OR apoplexy OR hemipleg* OR hemipar* OR subarachnoid) AND (mobilit* or function*) AND (predict* or prognos*)

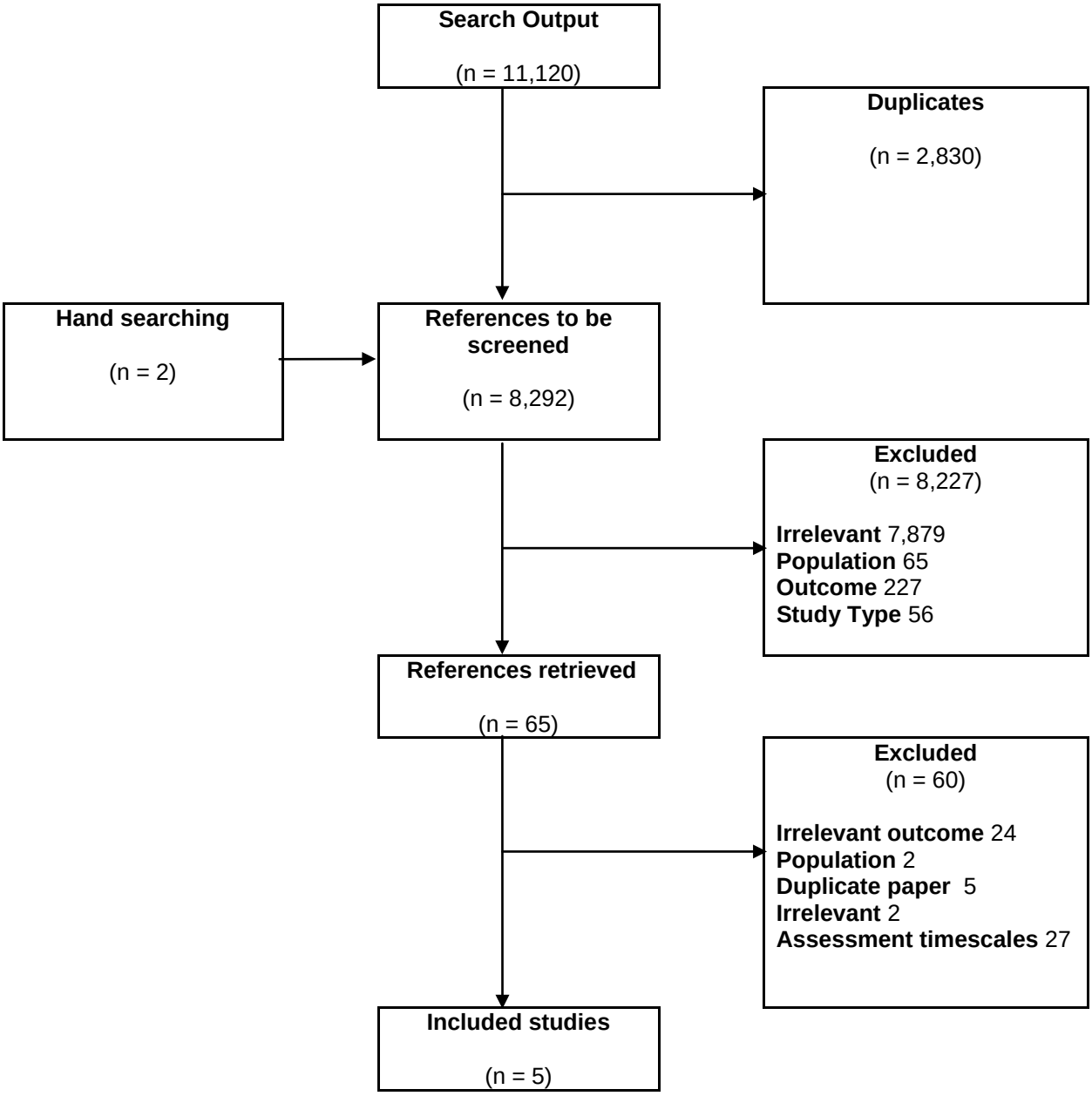
Latin American and Caribbean Health Sciences Literature (LILACS)

1. (("STROKE") or "CEREBROVASCULARDISEASE") or "CEREBROVASCULAR" or "CVA" [Words] and (((("MOBILITY")) or "FUNCTION")) or "PHYSICAL REHABILITATION") or "PHYSICALTHERAPY"

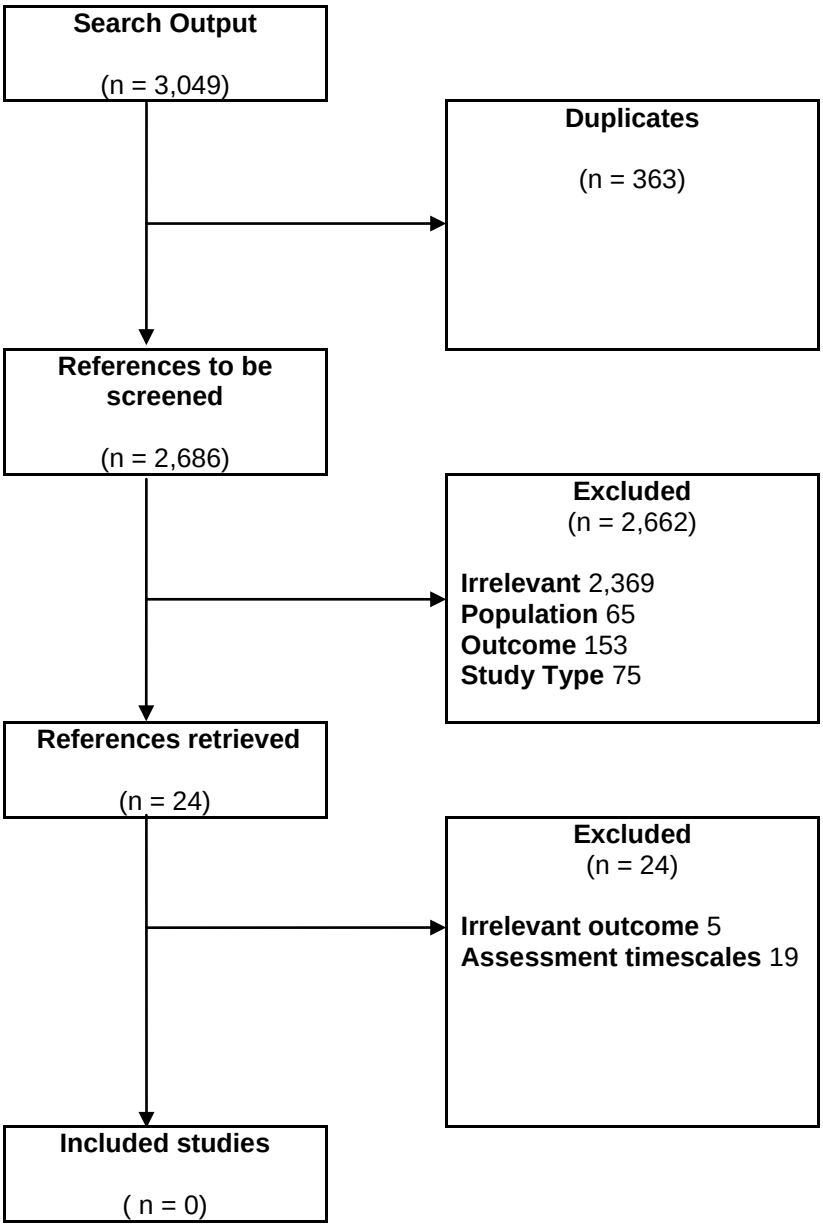
Electronic Table of Contents (ZETOC)

1. Stroke and mobility

Appendix 2 Search flow inception to July 2010



Appendix 3 Search flow updated



Appendix 4 Quality assessment of included studies

	Frideman 1990	Matsunga 1997	Baer & Smith2001	Jorgensen 1995	Smith 1999
External validity					
Community-based cohort	Yes	Yes	Yes	Yes	Yes
Included patients with TIA or SAH	No	No	No	No	No
Major exclusion criteria	No	No	No	No	No
Description of cohort provided	Yes*	Yes	Yes	Yes	Yes
Internal validity					
Inception cohort established	Yes	Yes	Yes	Yes	Yes
Adequate sample size	No	Yes	Yes	Yes	Yes
Baseline data collected prospectively	Yes	Yes	Yes	Yes	No
Outcomes valid and reliable	No	No	No	Yes	Yes
Fixed assessment time-point	Yes	Yes	No	No	No
Important predictors missed in the model	No	No	NA	NA	NA
Predictive variables clearly defined	Yes	No	Yes	Yes	Yes
Statistical validity					
The sample size adequate (EPV>10)	Yes	Yes	Yes	Yes	Yes
Stepwise regression was used	Yes**	No***	NA	NA	NA
Evaluation of the model					
The final model was internally validated	No	No	NA	NA	NA
The final model was externally validated	No	No	NA	NA	NA
Model predictions are better than clinical judgement	No	No	NA	NA	NA
The effect of the model assessed in clinical practice	No	No	NA	NA	NA
Practicality of the model					
The predictors are readily collected in practice	No	Yes	Yes	Yes	Yes
The coding of predictor variables was explained	No	Yes	NA	NA	NA
CIs were provided for the predictions	No	No	NA	NA	NA

TIA: Transient ischemic attack; SAH: Subarachnoid Haemorrhage; EPV: Events Per Variable

* The reporting of baseline demographics was stratified into mobile and non-mobile

** Backward selection; it was unclear the level of significance used

*** Multivariate analysis

Appendix 5 Factors selected by clinical opinion for model inclusion

Variable label	Description	Include	Exclusion*	Variable coding (as provided in data set)	Re-naming & coding (as entered in to model)
age	Age (years)	Y	-	Continuous	Continuous
gender	Gender	Y	-	1 = male, 2 =female	0 = female, 1 = male
doad	Date of hospital admission	N	2	-	-
recfloor	Ward number first admitted	N	2	-	-
timesyma	Time symptoms onset to admission (hrs)	Y	-	continuous	0 = ≤3.4 hours 1= >3.5 hours
housing	Living arrangements prior to admission	Y	-	1 = private address alone, 2 = private address not alone, 3 = sheltered housing, 4 = residential care, 5 = PNH, 6 = NHS, 7 = other	Alone, 0 = no, 1 = yes
psr	Level of disability prior to admission	N	3	-	-
psdepend	Level of dependency prior to admission	Y	-	1 = yes (RS 3 - 5), 2 = no (RS 0 - 2)	Independent pre-stroke, 0 = no, 1 = yes
hbp	History of hypertension	Y	-	0 = no, 1 = yes, 9 = not known	0 = no, 1 = yes (9 recoded no)
af	History of atrial fibrillation	Y	-	0 = no, 1 = yes, 9 = not known	0 = no, 1 = yes (9 recoded no)
miihdcf	History of myocardial infarction, ischemic heart disease or cardiac failure	Y	-	0 = no, 1 = yes, 9 = not known	0 = no, 1 = yes (9 recoded no)
dm	History of diabetes	Y	-	0 = no, 1 = yes, 9 = not known	0 = no, 1 = yes (9 recoded no)
pastcva	History of previous stroke	Y	-	0 = no, 1 = yes, 9 = not known	0 = no, 1 = yes (9 recoded no)
pasttia	History of previous TIA	Y	-	0 = no, 1 = yes, 9 = not known	0 = no, 1 = yes (9 recoded no)
smoker	Smoking status	Y	-	0 = not, 1 = current, 2 = ex-smoker, 9 = not known	Current smoker, 0 = no, 1 = yes
alcohol	Level of alcohol intake per week	N	1	-	-
antihbp	Current user antihypertensive medication	Y	-	0 = no, 1 = yes, 9 = not known	0 = no, 1 = yes (9 recoded no)
antiplat	Current user of antiplatlet medication	N	2	-	-
diuretic	Loop diuretic	N	2	-	-
anticoag	Current user of anticoagulant medication	Y	-	0 = no, 1 = yes, 9 = not known	0 = no, 1 = yes (9 recoded no)
diabmed	Current user of oral hypoglycaemic / insulin	N	3	-	-

* Reason for exclusion: 1: missing data; 2: irrelevant; 3: better measure available

Variable label	Description	Include	Exclusion*	Variable coding (as provided in data set)	Re-naming & coding (as entered in to model)
othermed	Current using of 'other medication'	N	1	-	-
sbpad	Systolic blood pressure on admission	Y	-	continuous	≤160mmH = 0, >160mmH = 1
dbpad	Diastolic blood pressure on admission	N	3	-	-
dysphag	Presence of dysphagia	Y	-	0 = no, 1 = yes	0 = no, 1 = yes
lesion	Side of lesion	Y	-	0 = not classifiable (n=35), 1 = left, 2 = right 3 = posterior	Left, 0 = no, 1 = yes
revocsp	Clinical classification of stroke type (OCSP)	Y	-	0 = not classifiable, 1 = TACS, 2 = PACS, 3 = LACS, 4 = POCS	TACS, 0 = no, 1 = yes
ctlesion	Stroke type based on CT results	Y	-	0 = no scan, 1 = no appropriate lesion visible, 2 = infarction, 3 = PICH, 4 = other	Haemorrhage, 0 = no, 1 = yes
daysct	Time to CT scan (days)	N	2		
consc0	Level of consciousness	N	4		
armpow0	Level of arm motor power	N	4		
hndpow0	Level of hand motor power	N	4		
legpow0	Level of leg motor power	N	4		
speech0	Level of speech	N	4		
palsy0	Level of facial palsy	N	4	-	-
urea0	Level of urea on admission	N	2	-	-
creat0	Level of creatinine on admission	N	2	-	-
gluc0	Level of glucose on admission	N	1	-	-
hb0	Level of haemoglobin on admission	N	1	-	-
wcc0	Level of white cell count on admission	N	1	-	-
floor	The location after ward admission	N	1	-	-
protocol	Use of stroke protocol	N	1	-	-
destday3	Hospital location of patient at day 3	N	1	-	-
maxtd12	Maximum temperature day 1 or 2	N	3		
maxsbp12	Maximum systolic BP day 1 or 2	Y	-	continuous	≤160mmH = 0, >160mmH = 1
minsbp12	minimum systolic BP day 1 or 2	Y	-	continuous	≤160mmH = 0, >160mmH = 1
maxdbp12	Maximum diastolic BP day 1 or 2	N	3	-	-

Variable label	Description	Include	Exclusion*	Variable coding (as provided in data set)	Re-naming & coding (as entered in to model)
mindbp12	Minimum diastolic BP day 1 or 2	N	3	-	-
o2day12	Minimum oxygen saturation day 1 or 2	N	2	-	-
na0_3	Maximum Na measured day 0 to 3	N	2	-	-
urea0_3	Max urea measured day 0 to 3	N	3	-	-
maxgl0_3	Max glucose measured day0-3	N	3	-	-
saline0	IV saline administered day 0	N	2	-	-
saline1	IV saline administered day 1	N	2	-	-
saline2	IV saline administered day 2	N	2	-	-
dext0	IV dextrose administered day 0	N	2	-	-
dext1	IV dextrose administered day 1	N	2	-	-
dext2	Iv dextrose administered day 2	N	2	-	-
para0_2	Doses of paracetamol provided day 0 to 2	N	2	-	-
antipla3	Antiplatelet administered on day 3	N	2	-	-
antibio3	Antibiotics administered on day 3	N	2	-	-
insulin3	Insulin administered on day 3	N	2	-	-
oxygen3	Oxygen saturation on day 3	N	2	-	-
advev	Adverse events recorded	N	3	-	-
modadve	Refined version of adverse events	Y	-	-	-
patpos3	Best level of mobility achieved by day 3	Y	-	1 = lying, 2 = sitting in bed, 3 = sit in chair, 4 =walking with help 5 = walking unaided	Walking 0 = no, 1 = yes
physio	Date of first assessment by physiotherapist	N	1	-	-
occther	Date of first assessment by occupational therapy	N	1	-	-
salt	Date of first assessment by speech and language	N	1	-	-
dateass3	Date of blinded assessment	N	2	-	-
patpos	Best level of mobility achieved by day 3	N	3	-	-
rankin3	Level of disability day 3	Y	-	0 = well, no symptoms, 1 =minor symptoms, 2 = minor handicap, 3 = moderate handicap, 4 = a lot of help, 5 = constant attention, 6 = death	Mild (3-6=0, 0-3=1) Moderate (0-3 & 6=0, 4=1) Severe (0-4 & 6=0, 5=1)

Variable label	Description	Include	Exclusion*	Variable coding (as provided in data set)	Re-naming & coding (as entered in to model)
consc3	Level of consciousness day 3	N	4	-	-
eyemvm3	Level of eye movements day 3	N	4	-	-
armpwr3	Level of arm motor power day 3	N	4	-	-
hndpwr3	Level of hand motor power day 3	N	4	-	-
legpwr3	Level of leg motor power day 3	N	4	-	-
orient3	Level of orientation day 3	N	4	-	-
speech3	Level of speech day 3	N	4	-	-
fapalsy3	Level of facial palsy day 3	N	4	-	-
gait3	Level of gait day 3	N	4	-	-
SSS3	Level of stroke severity (SSS) day 3	Y	-	continuous	Mild (0-42=0, 43-58=1) Moderate (0-26=0 & 41-58=0, 26-42=1) Severe (25-58=0, 0-25=1)
sssabre0	Level of stroke severity (level of consciousness, arm power, leg power, speech) day 0	N	3	-	-
sssabre3	Level of stroke severity (level of consciousness, arm power, leg power, speech) day 3	N	3	-	-
cathetr3	Use of catheter day 3	N	3	-	-
bowel3	Level of bowel function day 3	N	3	-	-
bladder3	Level of bladder function day 3	N	3	-	-
groom3	Level of grooming function day 3	N	3	-	-
toilet3	Level of toilet use day 3	N	3	-	-
feed3	Level of feeding day 3	N	3	-	-
transf3	Level of transfer day 3	N	3	-	-
walk3	Level of walking day 3	N	3	-	-
dress3	Level of dressing function day 3	N	3	-	-
stairs3	Level of stair climbing day 3	N	3	-	-
bath3	Level of bathing day 3	N	3	-	-

Variable label	Description	Include	Exclusion*	Variable coding (as provided in data set)	Re-naming & coding (as entered in to model)
bartot3	Level of activities of daily living (BI) day 3	Y		continuous	Mild (0-10 = 0, 10-20=1) Moderate (0-3 & 9-20 = 0, 3-9 = 1) Severe (3-20 = 0, 0-2=1)
ulf3	Upper limb function affect day 3	N	3	-	-
knf3	Use of knife and fork day 3	N	3	-	-
mug3	Ability to drink from mug day 3	N	3	-	-
comb3	Ability to comb hair day 3	N	3	-	-
card3	Ability to put on cardigan/jacket day 3	N	3	-	-
butn3	Ability to fasten buttons day 3	N	3	-	-
writ3	Ability to write name day 3	N	3	-	-

Appendix 6 Factors included in the multivariate models

Method of selection:	Systematic review (Model 1)	Clinical opinion (Model 2)	Univariate Analysis (Model 3)
Factors entered in model:	Age, Stroke type, Consciousness level, Leg power	Age, Gender, Housing arrangements, Pre-stroke dependency, Risk factors, History of stroke/transient ischemic attack, Smoking status, Antihypertensive medication, Presence of dysphagia, Side of lesion, Type of stroke, CT lesion, Maximum systolic blood pressure (day 1-2), Adverse events, Patient's best level of mobility (day 3), Stroke severity, Disability, Activities of daily living, Time from symptom onset to admission, Anticoagulant medication, Systolic blood pressure, Minimum systolic BP (day 1-2)	Age, Gender, Living alone, Pre-stroke dependency, Atrial fibrillation, History of stroke, Smoking status, Antihypertensive medication, Presence of dysphagia, Side of lesion, Type of stroke, CT lesion, Maximum diastolic blood pressure (day 1-2), Adverse events, Patient's best level of mobility (day 3), Stroke severity, Disability, Activities of daily living, Alcohol intake, Diabetic medication, Antiplatlets use prior to stroke (day 0), Maximum level of urea (day 0-3), Antiplatlets administered (day 3), Maximum systolic blood pressure (day 1 or 2), Maximum temperature (day 1 or 2), Minimum oxygen saturation (day 1 or 2), Maximum sodium level (day 3), Mean level of saline/dextrose administered (day 0-2), Mean level of dextrose administered (day 0-2), Antibodies administered (day 3), Insulin administered (day 3), Oxygen administered (day 3)

Appendix 7 Patient information sheet

Participant Information Sheet

Study Title:	**Physical activity levels after stroke**
Researcher Name:	Louise Craig
Researcher's contact details:	University of Glasgow Public Health and Health Policy 1 Lilybank gardens, Glasgow G12 8RZ Phone: 0141 330 7172 Mobile: 07810515504 Email: l.craig@clinmed.gla.ac.uk
Protocol Version	Version 2

The participant information sheet is **4** pages long. Please make sure you have all the pages.

Invitation paragraph

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Please talk to others about the study if you wish and ask if there is anything that is not clear or if you would like more information. Please take time to decide whether or not you wish to take part.

What is the purpose of the study?

The purpose of this study is to collect information about the amount of physical activity people who have had a stroke undertake during their acute hospital stay. Physical activity refers to bodily movement which uses up energy. The information from this study will be used to understand more about physical activity levels in stroke patients and how to monitor activity levels effectively.

Why have I been invited?

You are invited to participate in this research project because you have been diagnosed with a stroke within the last 14 days and are currently in a stroke ward. We are keen to include as many appropriate people as possible so that our results reflect normal care in a stroke ward.

Do I have to take part?

It is entirely up to you to decide whether or not you should take part. If you decide to take part, you will be asked to sign a consent form. You will be given copies of this information sheet and the consent form to retain. If you do decided to take part the researcher will write to your GP to let them know your involvement in the study. You will still be free to withdraw from the study at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect in any way the standard of care you will receive.

What will happen to me if I take part?

Your physical activity levels will be monitored for one day only during your stay in the stroke ward. A researcher will observe your activity throughout the day from 8.00am till 5.00pm. This will take place on the ward and the researcher will observe you for one minute every 10 minutes of the day. Information about who helped you with the activity and where the activity occurred will be recorded on a paper assessment sheet. There will be no audio or videotape record of your activity. The researcher will not come behind closed curtains or doors, however, the researcher may ask you or a staff member to tell them the nature of any activity not directly observed.

We will also use a small monitor to measure the time in minutes that you spend in activities such as sitting, standing and walking. The monitor is the size of a credit card and it will be attached on your thigh under your clothes using a specially designed sticky pad. This should not cause any discomfort or irritation. If it does, the monitor will be removed.

The same researcher who you meet in hospital will contact you by phone three months and six months after your stroke. You will be asked a few questions over the phone about how you are managing with certain activities since you have had your stroke. This will last about 20 minutes and will be done at a time which is convenient for you.

What will I have to do?

You will have nothing extra to do, apart from what has been explained above. You are not required to change your behaviour in any way on the day your activity is monitored. It is important that staff, family members and patients continue routine activities throughout this time.

What are the alternatives for diagnosis or treatment?

In this project we are not changing your treatment but collecting information about the care that you are currently receiving. If you choose not participate in this study, you will receive the current standard care for your medical condition.

What are the possible disadvantages and risks of taking part?

There is minimal risk in participating in this study. Should you find that you feel uncomfortable about being observed, you are free to talk to the study team or a member of the hospital and withdraw from the observation part of the study. If you find that wearing the monitor is uncomfortable you can ask a member of staff for this to be removed. Your hospital care will not be affected in any way whatsoever.

What are the possible benefits of taking part?

There are no direct benefits to you as a result of your participation in this study however your participation will help us understand more about how to monitor activity in stroke patients. This will allow any future changes in clinical practice which aim to affect activity levels in stroke patients to be detected.

What if new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, your doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your doctor will make arrangements for your care to continue. If you decide to continue in the study they may ask you to sign an updated consent form. If the study is stopped for any other reason, we will tell you and arrange your continuing care.

What happens when the research study stops?

This will make no difference to your treatment.

What if there is a problem?

The study is indemnified by the local hospital National Health Service (NHS) board, through whom you may be entitled to seek compensation. If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you have grounds for a legal action but you may have to pay for it. Regardless of this if you wish to complain about any aspect of the way you have been treated during the course of this study the NHS normal complaints mechanism may be available to you.

Will my taking part in the study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed. You will be provided with a study identification number.

What will happen if I don't want to carry on with the study?

You can withdraw from the study at any point. Information collected about you may still be used.

What will happen to the results of the research study?

The results of this study will be presented. The results may also be presented at conferences and written up in professional journals. You will not be identified in any report/publication. You will be provided with a copy of the study results if you wish.

Who is organising and funding the research?

Louise Craig is conducting this study and it is funded by a charity organisation called the Stroke Association.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by the Scotland A Research Ethics Committee.

Contact details of the researcher

Louise Craig
Stroke Association Research Fellow
University of Glasgow
Public Health and Health Policy
1 Lilybank gardens,
Glasgow G12 8RZ
Phone: 0141 330 7172
Mobile: 07810515504
Email: l.craig@clinmed.gla.ac.uk

Appendix 8 Patient consent sheet

Patient Consent Form

Study Title:	Physical activity levels after stroke
Researcher Name:	Louise Craig
Researcher's contact details:	University of Glasgow, Public Health and Health Policy 1 Lilybank gardens, Glasgow G12 8RZ Phone: 0141 330 7172 Mobile: 07810515504 Email: l.craig@clinmed.gla.ac.uk
Protocol Version	Version 2

Please place your initials in every box

1. I confirm that I have read and understand the information sheet 21st July 2010 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by a researcher from the University of Glasgow, from regulatory authorities or from the NHS Board, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in the study. ☐

5. I agree to take part in the above study. ☐

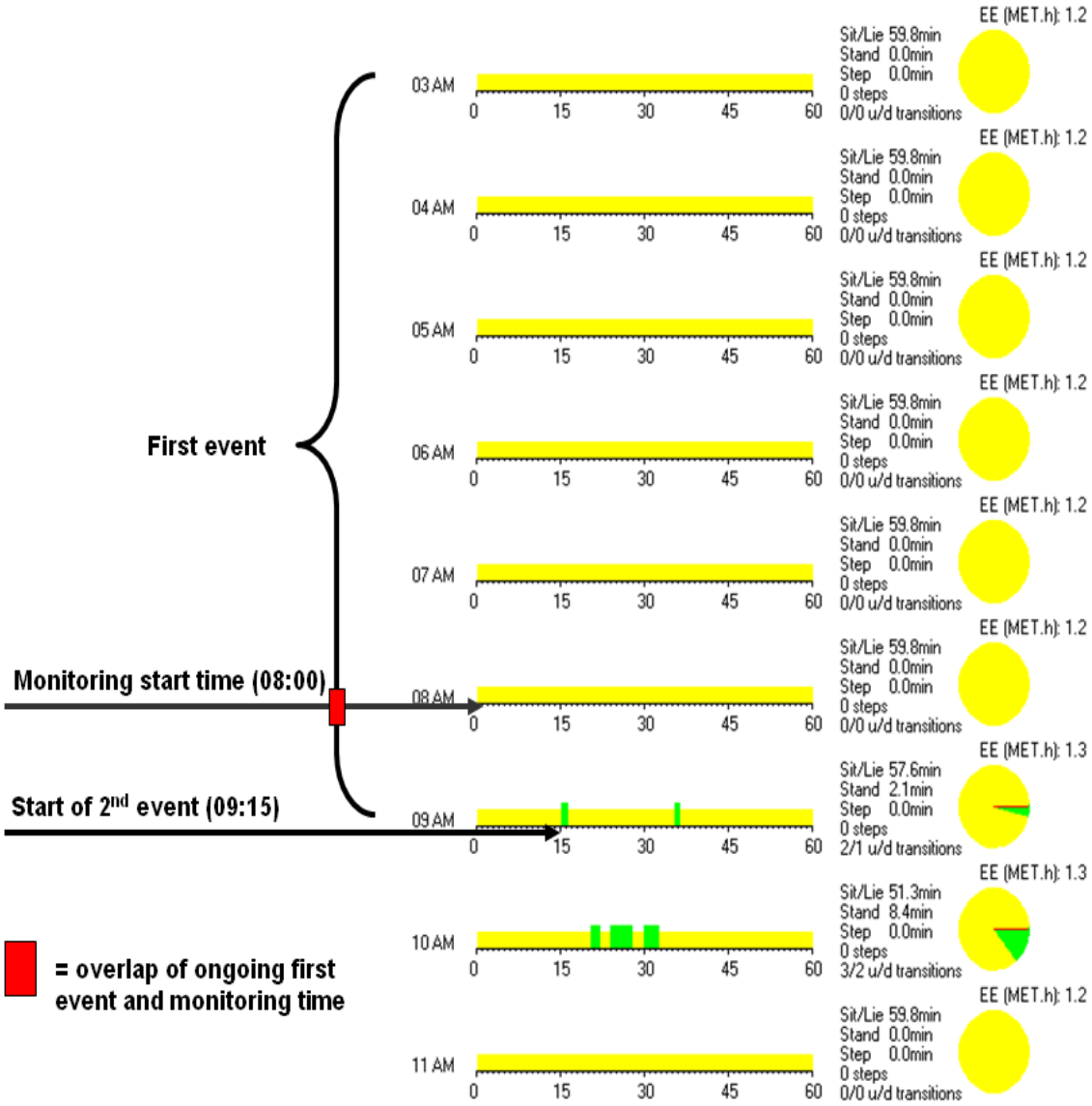
Name of Patient	**Date**	**Signature**
Name of Person taking consent (if different from researcher)	**Date**	**Signature**
Researcher	**Date**	**Signature**

Appendix 9 Definitions of summary accelerometer measures

Type of behaviour	Activity measure	Definition
Upright activity	Time spent upright	The proportion of time spent upright for each patient was calculated as follows: the total length of time spent in upright events (continuous periods of standing or walking)/total monitoring time x 100. A mean proportion was calculated to summarise group data. Times are presented as medians.
	Standing time	The total length of time spent in a standing posture.
	Walking time	The total length of time spent in a walking posture.
	Number of upright events	The total number of upright events.
	Number of standing events	The total number of standing event.
	Number of walking events	The total number of walking events.
	Number of transitions	The total number of changes between an upright and a sedentary posture (sit-to-stand plus stand-to-sit).
Sedentary	Time spent sedentary	The proportion of time spent sedentary for each patient was calculated as follows: the total length of time spent in sedentary events (continuous periods of lying or sitting)/total monitoring time x 100. A mean proportion was calculated to summarise group data. Times are presented as medians.
	Number of sedentary events	The total number of sedentary (continuous periods of lying or sitting) events in the period analysed. Summary estimate used was median time.
Upright activity and sedentary	Accumulation of upright and sedentary episodes	Each sedentary event and upright event were classified into one of the following time intervals: < 5 minutes, 5 to 10 minutes, 10 to 30 minutes, 30 to 60 minutes, > 60 minutes). The percentage of total time spent upright and sedentary for each time interval was then calculated.

All times are in minutes

Appendix 10 Example accelerometer output



In the example above the first event overlaps the start time. The amount of time spent in this event after 08:00 was 9% (75.2 minutes) of the total event time. Using the decision rule to exclude events that were spent more than 50% of time outside the monitoring period would result in 13.9% of the data being excluding for this patient and would result in an underestimation of time spent. Yellow colour represents sitting/lying. Green colour represents standing. An event is defined as a continuous period of activity.

Appendix 11 Participant information sheet

Participant Information Sheet

Study Title:	Exploring the Implementation of Very Early Mobilisation in Acute Stroke Care
Researcher Name:	Louise Craig
Protocol Version	Version 2

The participant information sheet is **3** pages long. Please make sure you have all the pages.

Invitation paragraph

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully and talk to others about the study if you wish. Ask the researcher if there is anything that is not clear or if you would like more information. Take your time to decide whether or not you wish to take part. Louise Craig is a Research Fellow based at the University of Glasgow and will be conducting this study in part fulfilment of a research degree.

What is the purpose of the study?

The purpose of this study is to understand more about the current process of care in an acute stroke unit such as early rehabilitation and also to hear your views on how new guidelines are introduced into your units. This will add to our understanding about how research findings can be implemented into real clinical practice more smoothly. In order to hear your views multidisciplinary discussion groups known as focus groups will be conducted.

Why have I been invited to participate in the study?

You are invited to participate in this research project because you are currently working in an acute stroke unit in Scotland and delivering care to acute stroke patients. We are keen to include as many healthcare professionals and assistants so that our findings are representative of National Health Service staff working in acute stroke units in Scotland. Also, the more people who take part the better, as the information collected and the findings from the research can be used with more confidence.

Do I have to take part?

It is entirely up to you to decide whether or not you should take part. If you decide to take part, you will be asked to sign a consent form and provide your contact details so that the researcher can be in touch with you. You will be given copies of this information sheet and the consent form to retain. You will still be free to withdraw from the study at any time and without giving a reason.

What will happen to me if I take part?

If you do decide to take part the researcher will write to you to confirm a date, time and location which you have pre-specified as convenient to you. You will only have to attend one of the eight focus groups being set up which is likely to be the one held in your place of work. There will be up to eight participants in each of the groups. During the focus group the researcher will ask a number of questions which you will discuss as a group. You will be encouraged to talk freely and listen to other participants in the group. You will be reminded that there are no right or wrong answers to the questions. The expected length of the focus group is one and a half hours. All group discussions will be recorded using a dictaphone so that what you say can be recorded accurately and can be typed up at a later date. A few weeks after you have participated in the focus group you will be sent a copy of the transcript to ensure that you are happy that it is a true interpretation of what was discussed. No information that could lead to your personal identification will be released, reported or published. Statements from the focus groups that illustrate particular themes or issues may be included in published outputs. You will be asked to indicate any of your sections on the proof transcript that you would not want include in any of these outputs. The sections you indicate will remain confidential.

What are the possible disadvantages and risks of taking part?

There is minimal risk in participating in this study. Should you feel uncomfortable at any point during the focus group, you are free to withdraw from the study. Your contribution in the focus group will be included in the final focus group data analysis.

What are the possible benefits of taking part?

There are no direct benefits to you as a result of your participation in this study however your participation will help us understand more about the processes of care such as early rehabilitation for acute stroke patients and will improve our understanding about how new guidelines and procedures can be more easily implemented into acute stroke units.

What if there is a problem?

The study is indemnified by the local hospital National Health Service (NHS) board, through whom you may be entitled to seek compensation. If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you have grounds for a legal action but you may have to pay for it. Regardless of this if you wish to complain about any aspect of the way you have been treated during the course of this study the NHS normal complaints mechanism may be available to you.

Will my taking part in the study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. No names will be used in reports or publications. You will be provided with a study identification number. The audio recordings made during this research will be used only for analysis and for illustration in publications. No other use will be made of them without your written permission, and no one outside the project will be allowed access to the original recordings.

What will happen if I don't want to carry on with the study?

You can withdraw from the study at any point. Information collected about you may still be used.

What will happen to the results of the research study?

The results may be presented at conferences and written up as a report and in professional journals. You will not be identified in any report/publication. You will be provided with a copy of the study results if you wish.

Who is organising and funding the research?

Louise Craig is conducting this study and it is funded by a charity organisation called the Stroke Association.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by West of Scotland Research Ethics Committee.

Contact details of the researcher

Louise Craig
Stroke Association Research Fellow
University of Glasgow
Public Health and Health Policy
1 Lilybank gardens,
Glasgow G12 8RZ
Phone: 0141 330 7172
Mobile: 07810515504
Email: Louise.Craig@glasgow.ac.uk

Appendix 12 Participant consent sheet

Participant Consent Sheet

Study Title:	Exploring the Implementation of Very Early Mobilisation in Acute Stroke Care
Researcher Name:	Louise Craig
Protocol Version	Version 2

Please place your initials in every box

1. I confirm that I have read and understand the information sheet 29th September 2010 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason ☐

3. I understand that the focus groups will be audio-taped and that the data collected and held about me will be confidential and stored securely ☐

4. I agree to the use of anonymised quotes from the group discussion illustrating particular themes or issues being included in published outputs. I understand that the proof transcript that I receive will ask me to indicate any of the sections that I do not want included in any of these outputs. These sections which I indicate will remain confidential. ☐

5. I agree to take part in the above study ☐

Name of Participant	Date	Signature

Name of Researcher	Date	Signature

Appendix 13 Interview schedule

Focus Group Schedule (version with prompts)

1. Can you tell me what happens to a stroke patient from hospital arrival to their admission to the stroke unit?
What is the referral process? Who is involved in this referral process?
What criteria are used to decide whether or not a patient is to be cared for in an acute stroke unit?
Are all stroke cases admitted to the stroke unit? If not, do you see any reason for this?
How well do you think the referral pathways works?
Can you suggest any improvements in this referral process?

2. What do you think is good about what you do in the stroke unit?
What is good about how care is organised on your unit? (*Communication, MDT working, discharge planning…..)*
What are the strengths of the staffing arrangements for the stroke service in this hospital?
In what ways do you think the stroke service in this hospital could be improved?

3. At what point after admission to the stroke unit do you decide to get a patient out of bed for the first time?
What influences your decision to mobilise a patient for the first time?
Who usually gets the patient out of bed for the first time?
-why do you think it is this particular profession/individual that carries this out?
Does this vary depending on the time of day the patient is admitted to hospital or if it is at the weekend?
Do you see any issues with the current practice around mobilising the patient for the first time?

4. After this first mobilisation, how do you go about mobilising the patient for the rest of their stay?
How often in a day would the patient be mobilised by staff?
- do you think this is enough?
Who is involved in the mobilisation of patients?
-how do you communicate the patient's mobility within the team?
Do you see any issues with mobilising patients in the unit?

5. What do you think would happen if a patient was not mobilised during their time in the stroke unit?
How do you think this would impact on the patient's recovery?
-how do you think the patient would view this?
What effect do you think this would have on the unit?
Very Early Mobilisation is a topical area at the moment. By very early mobilisation I mean mobilising patients within 24 hours of stroke onset and continuing mobilisation at an increased frequency throughout their time in the stroke unit.

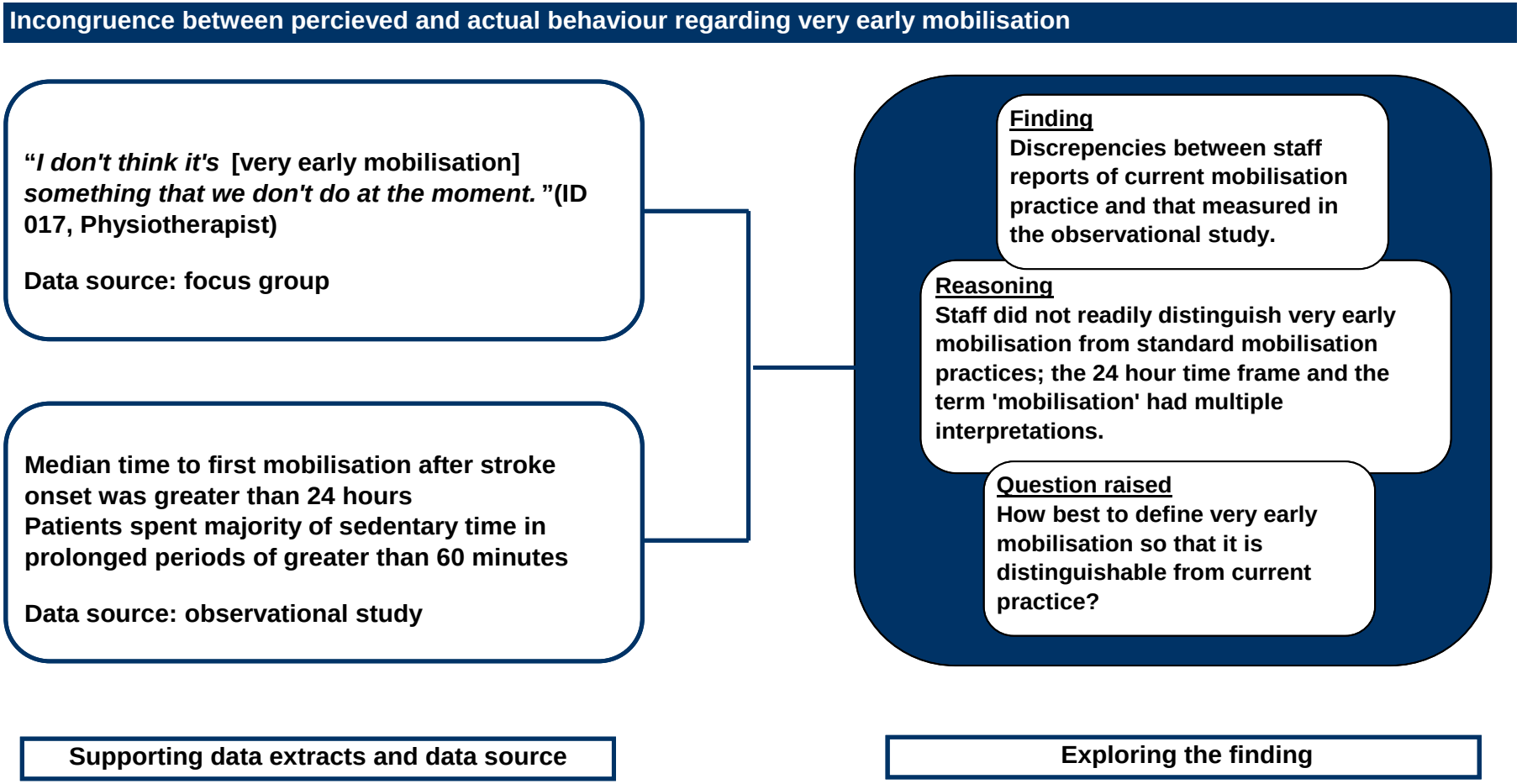
6. What do you think about mobilising patients within 24 hours after their stroke?
Do you think it is beneficial for patients? If so, what do you think the benefits are?
Do you think there any risks? If so, what do you think these risks are?
What you think about mobilising patients more frequently than they currently are?
I am also interested in what you think about very early mobilisation and other mobilisation strategies for different types of patients. I provided a list of scenarios that you rated in terms of appropriateness before you came to the group and now I would like to discuss these ratings.

7. Imagine that next week in the unit you had to start mobilising patients within 24 hours of stroke onset what would you need to do this?
What would help this process?
-who would you need involved?
What do you see as the barriers to implementing mobilising patients within 24 hours of stroke onset?
And as for mobilising patients more frequently what would you need to do this?

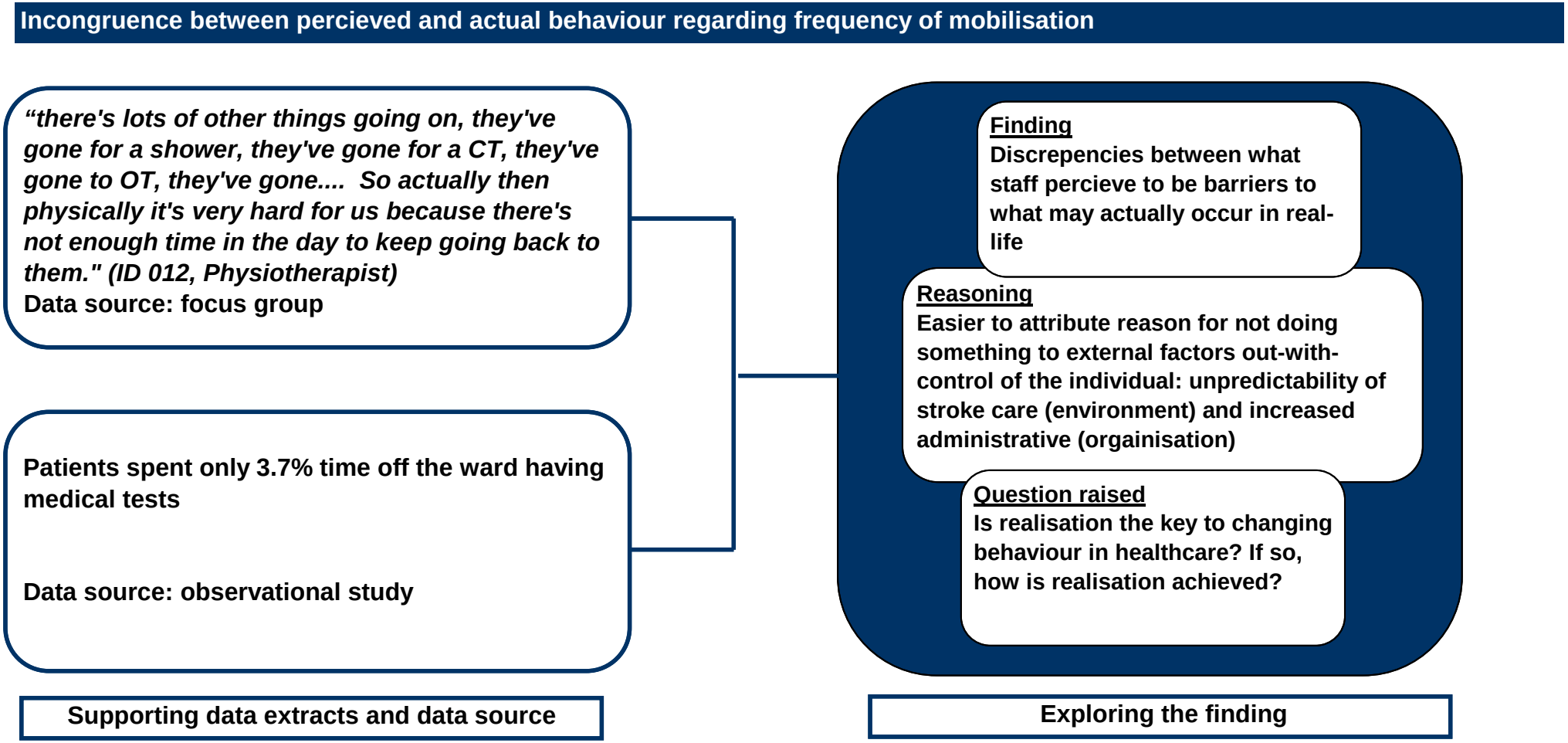
Focus Group Schedule (version with prompts)

What do you see as the barriers to implementing mobilising patients within 24 hours of stroke onset?
-what do you think the patient would think of this?
Research into stroke care is going on all the time. I am interested in hearing about how some of these may have changed your practice.
8. Have there been any changes in stroke practice that you think have been particularly good?
(specific example headings may include organisation and staff structure and positions, education, methods of communication, referral systems, protocols, decision management)
Can you explain how this change came about?
How did it impact on how you would normally do things?
Who was involved in this change?
Did anything help you/the unit to make this change?
-new equipment/staff
What do you think were the barriers to change?
-do you think other members of the team felt the same?
Did you see this change benefit patients?
9. There are a number of different approaches being used in healthcare to assist with changing practice. I am going to describe two of these and would like your views on both.
i)Having a local champion that is someone in the organisation who knows how things work and is passionate about the change?
-have you heard or used this strategy been used before?
-how well do you think that this would work in your unit/local area
Do you think such an approach would benefit the implementation of very early mobilisation, given it was shown to be effective?
ii) Using *quality circles* that is meeting as a group to discuss current problem areas, successes and
failures?
-have you heard or used this strategy been used before?
-how well do you think that this would work in your unit/local area
- do you think such an approach would benefit the implementation of very early mobilisation, given it was shown to be effective?
10. What do you consider to be the three most important key aspects to stroke care in your unit?
11. Have I missed anything that you would like to add?

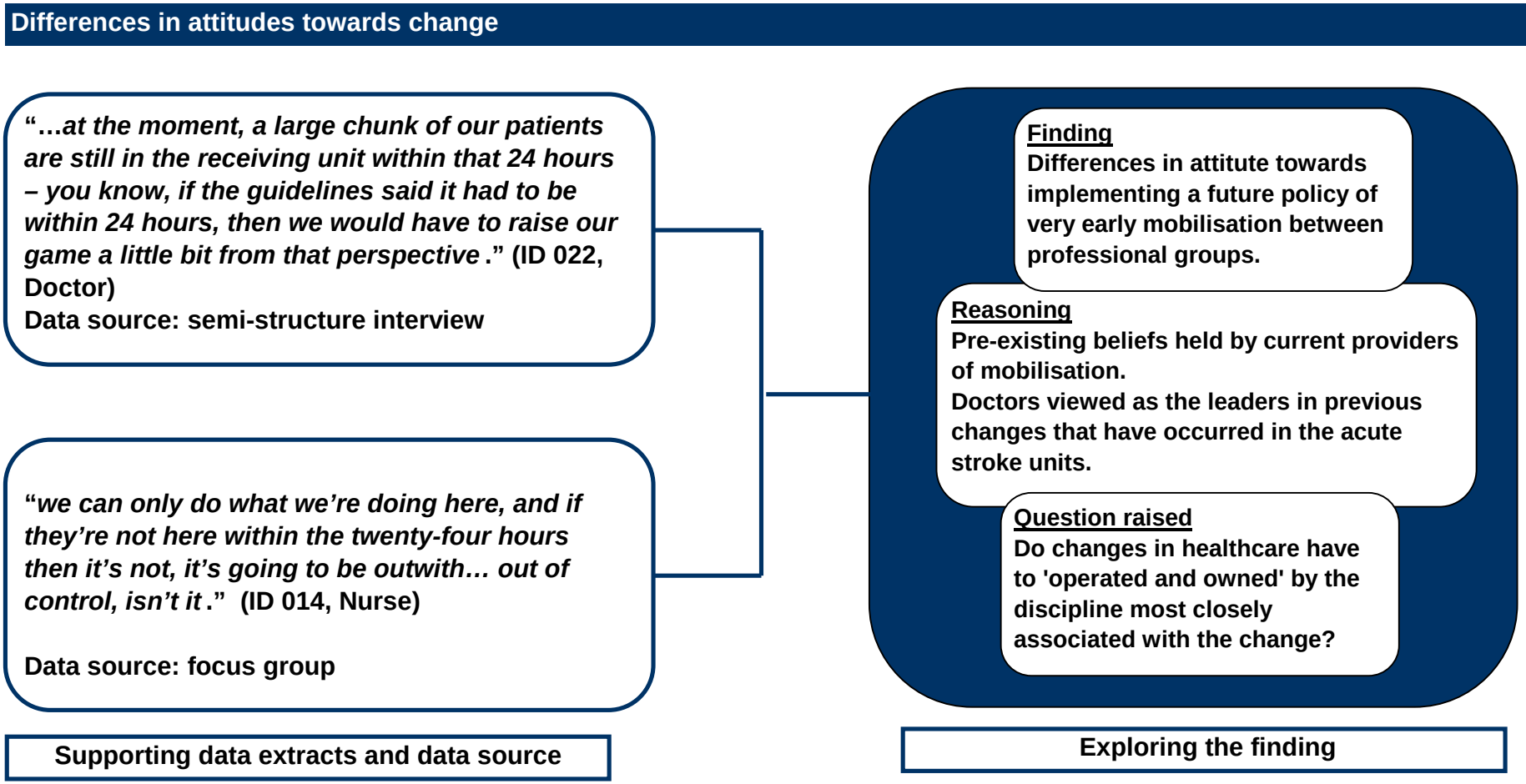
Appendix 14 Incongruence between perceived and actual behaviour (1)



Appendix 15 Incongruence between perceived and actual behaviour (2)



Appendix 16 Differences in attitude between professional groups



Appendix 17 Search strategies for databases (Chapter 6)

Medical Literature Analysis and Retrieval System Online (Medline)

1. exp cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp basal ganglia hemorrhage/ or exp brain ischemia/ or exp brain infarction/ or exp brain stem infarctions/ or exp cerebral infarction/ or exp infarction, anterior cerebral artery/ or exp infarction, middle cerebral artery/ or exp infarction, posterior cerebral artery/ or exp hypoxia-ischemia, brain/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or exp cerebral hemorrhage/ or exp subarachnoid hemorrhage/ or stroke/
2. ((cerebral* or cerebellar or brainstem or vertebrobasilar or stroke) adj5 (infarct* or ischaemi* or ischemi* or thrombo* or emboli* or apoplexy)).tw.
3. hemiplegia/ or exp paresis/
4. (hemipleg* or hemipar* or paresis or paretic).tw.
5. (stroke or cva* or cerebral vascular accident* or cerebrovascular accident*).tw.
6. ((cerebral or brain or subarachnoid) adj5 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)).tw.
7. Economics/ or "costs and cost analysis"/
8. Cost allocation/ or Cost-benefit analysis/
9. Cost control/ or Cost savings/
10. Cost of illness/ or Cost sharing/
11. "deductibles and coinsurance"/ or Medical savings accounts/
12. Health care costs/ or Direct service costs/
13. Employer health costs/

14. Hospital costs/ or Health expenditures/

15. Capital expenditures/ or Value of life/

16. exp economics, hospital/ or exp economics, medical/

17. Economics, nursing/ or Economics, pharmaceutical/

18. exp "fees and charges"/ or exp budgets/

19. (low adj cost).mp.

20. (high adj cost).mp.

21. (health?care adj cost$).mp.

22. (fiscal or funding or financial or finance).tw.

23. (cost adj estimate$).mp.

24. (cost adj variable).mp.

25. (unit adj cost$).mp.

26. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.

27. 1 or 2 or 3 or 4 or 5 or 6

28. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

29. 27 and 28

30. rehabilitation/ or occupational therapy/ or physical therapy techniques/

31. "Physical Therapy (Speciality)"/ or exercise therapy/ or exercise movement techniques/ or exercise/

32. early ambulation/ or " Physical Education and Training"/ or Physical Fitness/ or "Recovery of Function"/

33. Rehabilitation Nursing/ or "Activities of Daily Living"/ or "Physical Education and Training"/ or Physical Fitness/
34. (rehabilitat$ or exercise$ or physiotherap$).tw.
35. (Physical adj3 (therp$ or education or activit$ or function)).tw.
36. (Physical adj3 (therap$ or education or activit$ or function)).tw.
37. (improve$ adj3 (function or mobil$ or recover$)).tw.
38. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39. 29 and 38

Embase Search Strategy

1. exp cerebrovascular disease/ or exp basal ganglia hemorrhage/ or exp brain ischemia/ or exp brain infarction/ or exp brain hematoma/ or exp brain stem infarctions/ or exp brain hemorrhage/ or exp cerebral artery disease/ or exp brain embolism/ or exp subarachnoid hemorrhage/ or exp stroke/
2. ((cerebral* or cerebellar or brainstem or vertebrobasilar or stroke) adj5 (infarct* or ischaemi* or ischemi* or thrombo* or emboli* or apoplexy)).tw.
3. exp hemiplegia/ or exp paresis/
4. (hemipleg* or hemipar* or paresis or paretic).tw.
5. (stroke or poststroke or post-stroke or cva* or cerebral vascular accident* or cerebrovascular accident*).tw.
6. ((cerebral or brain or subarachnoid) adj5 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)).tw.
7. Socioeconomics/
8. Cost benefit analysis/
9. Cost effectiveness analysis/

10. Cost of illness/
11. Cost control/
12. Economic aspect/
13. Financial management/
14. Health care cost/
15. Health care financing/
16. Health economics/
17. Hospital cost/
18. (fiscal or financial or finance or funding).tw.
19. Cost minimization analysis/
20. (cost adj estimate$).mp.
21. (cost adj variable$).mp.
22. (unit adj cost$).mp.
23. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 1 or 2 or 3 or 4 or 5 or 6
25. 23 and 24
26. rehabilitation care/ or rehabilitation nursing/ or rehabilitation/ or rehabilitation patient/ or community based rehabilitation/ or rehabilitation medicine/
27. physiotherapy/
28. occupational therapy/
29. exercise recovery/ or movement therapy/

30. (rehabilitat$ or exercise$ or physiotherap$).tw.

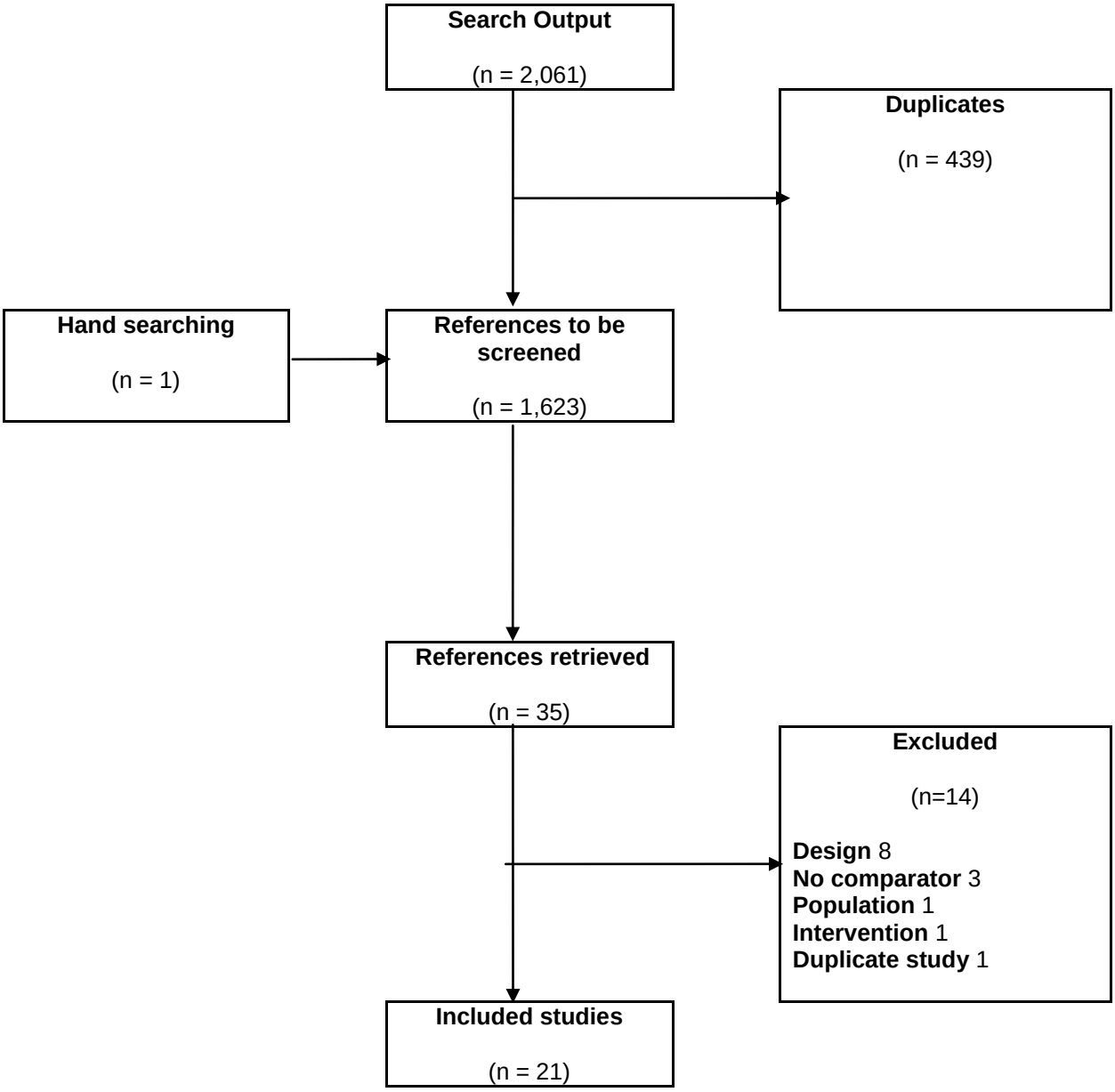
31. (Physical adj3 (therap$ or education or activit$ or function)).tw.

32. (improve$ adj3 (function or mobil$ or recover$)).tw.

33. 26 or 27 or 28 or 29 or 30 or 31 or 32

34. 25 and 33

Appendix 18 Search flow inception to September 2011



Appendix 19 Table of evidence of included studies (Chapter 6)

Author (location)	Study type	Comparison	Perspective	Source of effectiveness data	Source/method of costing	Uncertainty	Measures of benefit*	Synthesis of costs & benefits
Anderson et al 2000 New Zealand	CMA	ESD service versus home-based rehabilitation	Health service & carers	Single RCT study n=86 6 months	Health service: individual resource use from study (where not possible average costs were applied), costs from hospital finance (included overheads), national unit costs Caregivers: study questionnaire	Yes	Clinical outcomes: HRQoL (SF-36), general health, physical function, social activities, family dynamics, emotional state, the Caregiver Strain Index were administered to caregivers. Use of community services, readmissions to hospital, history of falls, place of residence, and patient and caregiver satisfaction with their medical care, rehabilitation and recovery	NA

Author (location)	Study type	Comparison	Perspective	Source of effectiveness data	Source/method of costing	Uncertainty	Measures of benefit*	Synthesis of costs & benefits
Beech et al 1999 UK	CMA	Community based care versus standard inpatient	Not explicitly reported (health service & social care assumed)	Single RCT study n=331 12 months	Health service: individual resource use from study (38 patients only), costs from hospital finance Social services: study questionnaire, costs based on PSSRU	Yes	Clinical outcomes: Impairment, disability, general health, caregiver stress and patient and caregiver satisfaction.	NA
Bjorkdahl et al 2006 Sweden	CCA	Home rehabilitation versus outpatient rehabilitation	Not explicitly reported (health service assumed)	Single RCT study n=59 12 months	Health service: costs of delivering the intervention (assumed treatment length, therapy salary & travel), cost based on therapy salary, hospital finance & authorities	No	Clinical outcomes: Motor and process skills, functional independence measure and dependence in activities of daily living.	NA
Chen et al 2006 China	CEA	Three-stage rehabilitation program with no rehabilitation training	Societal	Single RCT study n=70 6 months	Health service: direct medical costs (method of costing not reported) Indirect expenses (transport, special diet, carer costs patients and loss of productivity).	No	Clinical outcomes: motor (FMA), ADL (BI), function (FCA) , cognition (CFS) and neurological deficit (NDS) All outcomes were used in the economic analysis.	ICER (cost per score increase on each of the outcomes)

Author (location)	Study type	Comparison	Perspective	Source of effectiveness data	Source/method of costing	Uncertainty	Measures of benefit*	Synthesis of costs & benefits
Donnelly et al 2004 UK	CCA	Community stroke team with hospital rehabilitation	Health service	Single RCT study n=113 12 months	Health service: individual patient resource use (38 patients only), costs based on hospital finance Social care: individual patient resource use, costs based on PSSRU	No	Clinical outcomes: HRQoL (SF-36), activities of daily living, patient and carer satisfaction.	NA
Gladman et al 1994 UK	CMA	Community-based rehabilitation versus hospital based rehabilitation	Health service	Single RCT study n=327 6months	Health service: total intervention (therapists salary & travel) & hospital admissions, costs based on hospital finance & ambulance service	No	Clinical outcome: HRQoL (Nottingham Health Profile), activities of daily living, carer satisfaction and life engagement	NA
Harrington et al 2010 UK	CMA	Community-based exercise and education scheme	Health service, social services & carers	Single RCT study n=243 12 months	Health service: individual patient resource use, costs based on national unit costs, BNF Social care: individual patient resource use, costs based on PSSRU Personal: individual patient resource use, costs self-reported & AA schedule	No	Clinical outcome: HRQoL (WHOQoL-Bref), social and physical outcome, mobility, activities of daily living, carer strain, functional reach and mobility and depression	NA

Author (location)	Study type	Comparison	Perspective	Source of effectiveness data	Source/method of costing	Uncertainty	Measures of benefit*	Synthesis of costs & benefits
Huijbregts et al 2008 Canada	CEA	Self-management program with land & water exercise versus a standard education program	Health service	Single non-randomised trial n=30 3 months	Health service: individual patient resource use, costs based on personnel costs Personal: charge of program to individual & carer	No	Clinical outcomes: *balance (ABC), re-integration into normal living scale (RNL)* , function, depression, physical performance	The cost per mean point improvement on the ABC scale & RNL index
Keith et al 1995 USA	CEA	Acute rehabilitation versus sub-acute rehabilitation facility	Not reported (health service assumed)	Single retrospective cohort n=428 discharge	Health service costs: charge data for a stay was used as a proxy	No	Clinical outcomes: successful discharge and functional gain	The average cost per successful case for patients returned to the community and the cost of functional gain
Larson et al 2006 Denmark	CCA	ESD service versus conventional rehabilitation	Not reported (health service assumed)	Systematic review and meta-analysis	Costing data was based on the individual economic analyses. The average number of visits in the trials multiplied by assumed time. Unit costs: international unit standard	No	Odds of poor outcome and the number of patients need-to-treat	No

Author (location)	Study type	Comparison	Perspective	Source of effectiveness data	Source/method of costing	Uncertainty	Measures of benefit*	Synthesis of costs & benefits
McNamee et al 1998 UK	CCA	ESD service versus conventional care	Healthcare service	Single RCT study n=92 6 months	Health service costs: individual patient resource use Social care costs: medical records	Yes	Clinical outcomes: ADL, depression, general health	No
Roderick et al 2001 UK	CCA	Community-based rehabilitation versus geriatric hospital	Health service and social service	Single RCT study n=140 6 months	Health service costs: individual patient resource use, costs based on hospital trust financial returns, national unit costs, ambulance service Social care costs: PSSRU	Yes	Clinical outcomes: HRQoL (SF-36), functional gain, mobility, mental state and social activity.	NA
Rodgers et al 2003 UK	CMA	Increased-intensity interdisciplinary upper limb programme versus standard care	Health service and social services	Single RCT study n=123 6 months	Health service costs: individual patient resource use, costs based on national unit costs Social care costs: national unit costs	No	Clinical outcomes: impairment, upper limb function, disability and upper limb pain.	NA
Sritipsukho 2010	CEA	Home rehabilitation program versus conventional care	Health service	Single RCT study n=60 12 months	Health service costs: individual patient resource use, costs based on reimbursement rate	Yes	Clinical outcomes: HRQoL (EQ-5D) and *disability*	ICER (disability averted as measure of effect)
Tay-Teo et al 2008 Australia	CEA	Very early mobilisation versus standard care	Societal	Single RCT study n=71 3 months	Health service costs: individual patient resource use, costs based on national unit costs Social services: individual patient resource use, an annuity in arrears was applied	Yes	Clinical outcomes: death, serious adverse events, stroke deterioration and perceived exertion	ICER (cost per good outcome used as measure of effect)

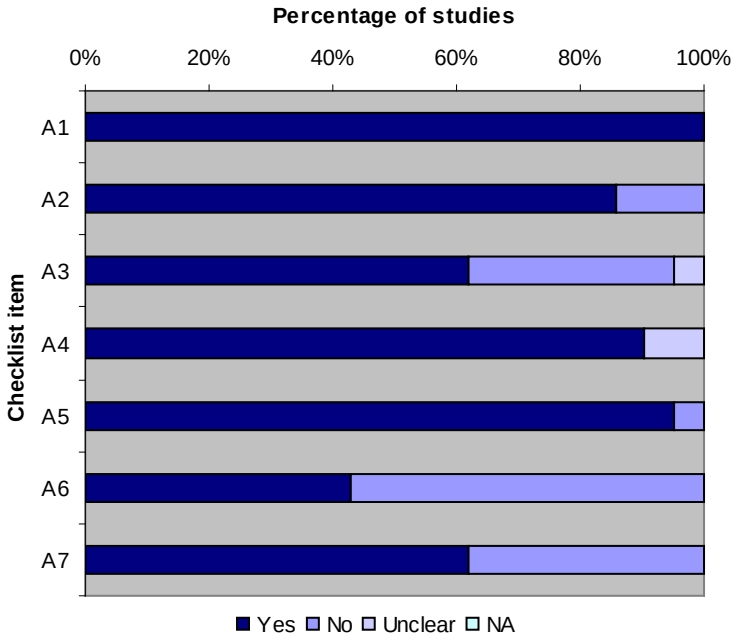
Author (location)	Study type	Comparison	Perspective	Source of effectiveness data	Source/method of costing	Uncertainty	Measures of benefit*	Synthesis of costs & benefits
					to estimate costs for 5 year usage of modifications & equipment Productivity costs: human capital approach			
Teng et al 2003 Canada	CCA	ESD versus standard care	Health service	Single RCT study n=114 3 months	Health service costs: individual patient resource use, costs based on hospital finance (included overheads) Social services: individual patient resource use, costs based on local community finance records	Yes	Clinical outcomes: HRQoL (SF-36), impairment, activities of daily living, mobility, reintegration into normal life and community living	NA
Von Koch et al 2001 Sweden	CCA	ESD versus standard care	Not explicitly reported (health service assumed)	Single RCT study n=83 12 months	Health service: individual patient resource use, costs based on council and national social insurance board	No	Clinical outcomes: mortality, motor capacity, dysphasia, activities of daily living, social activities, perceived dysfunction and self-reported falls.	NA
Widen Holmqvist et al 1996 Sweden	CCA	ESD versus hospital	Health service & carers	Single non-randomised trial n=27 12months	Health service: individual patient resource use, costs based on council registers, market prices of equipment Social care: individual patient resource use, costs based on	No	Clinical outcomes: HRQoL (Sickness Impact Profile), patient satisfaction and dependency in	NA

Author (location)	Study type	Comparison	Perspective	Source of effectiveness data	Source/method of costing	Uncertainty	Measures of benefit*	Synthesis of costs & benefits
					market prices of equipment, salary of home-helps Carers: individual patient resource use, costs based on home-help equivalent		activities in daily living	
Xiao 2004	CEA	Comprehensive rehabilitation group versus a conventional rehabilitation group	Societal	Single randomised trial n=116 2 weeks	Health service: total hospital charge Patient and carers: loss of productivity	No	Clinical outcomes: ADL and neurological deficit (NDS)	ICER (ADL and neurological deficit scores)
Yagura et al 2005 Japan	CCA	Stroke rehabilitation unit compared with a general rehabilitation ward	Health service	Single RCT study n=178 3 months	Health service: individual patient resource use, source of costs not explicitly stated	No	Clinical outcomes: disability, neurological impairment and discharge disposition.	NA
Young and Forster 1993 UK	CMA	Day hospital care and home physiotherapy	Health service, social services carer	Single RCT study n=124 6 months	Health service: individual patient resource use Social care: individual patient resource use	No	Clinical outcomes: HRQoL (Nottingham health profile), ADL, motor impairment, carer stress	NA

* Outcomes that are in italic refer to those that were used in the economic evaluation

ESD: Early Supported Discharge; RCT: Randomised Controlled Trial; HRQoL: Health Related Quality of Life; SF-36: Short-Form 36 Health Survey: PSSRU; Personal Social Services Research Unit; FMA: Fugl-Meyer Motor Assessment; ADL: Activities of Daily Living; BI: Barthel Index; FCA: Function Comprehensive Assessment; CFS; Cognitive Function Score; NDS: Neurological Deficits Scores; BNF: British National Formulary; AA: Automobile Association; ABC: Activities-Specific Balance Scale; RNL; Reintegration to Normal Living Index: EQ-5D: Euroqol-5D; ICER: Incremental Cost-Effectiveness Ratio

Appendix 20 Quality assessment – study design

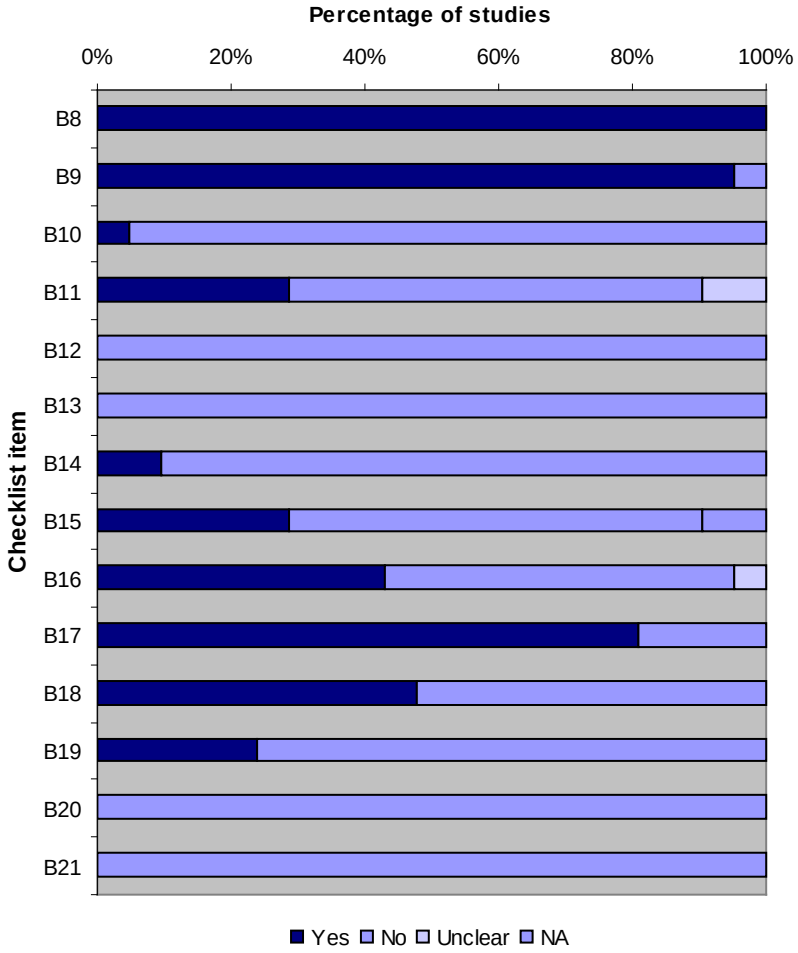


Checklist item	Quality statement
A1	The research question is stated.
A2	The economic importance of the research question is stated.
A3	The viewpoint(s) of the analysis are clearly stated and justified.
A4	The rationale for choosing alternative programmes or interventions compared is stated.
A5	The alternatives being compared are clearly described.
A6	The form of economic evaluation used is stated.
A7	The choice of form of economic evaluation is justified.

Key findings (n=21):

- The viewpoint of the analysis was stated in 13 studies
- The form of the economic evaluation was stated in 9 studies
- The choice of the type of economic evaluation was justified in 13 studies

Appendix 21 Quality assessment – data collection

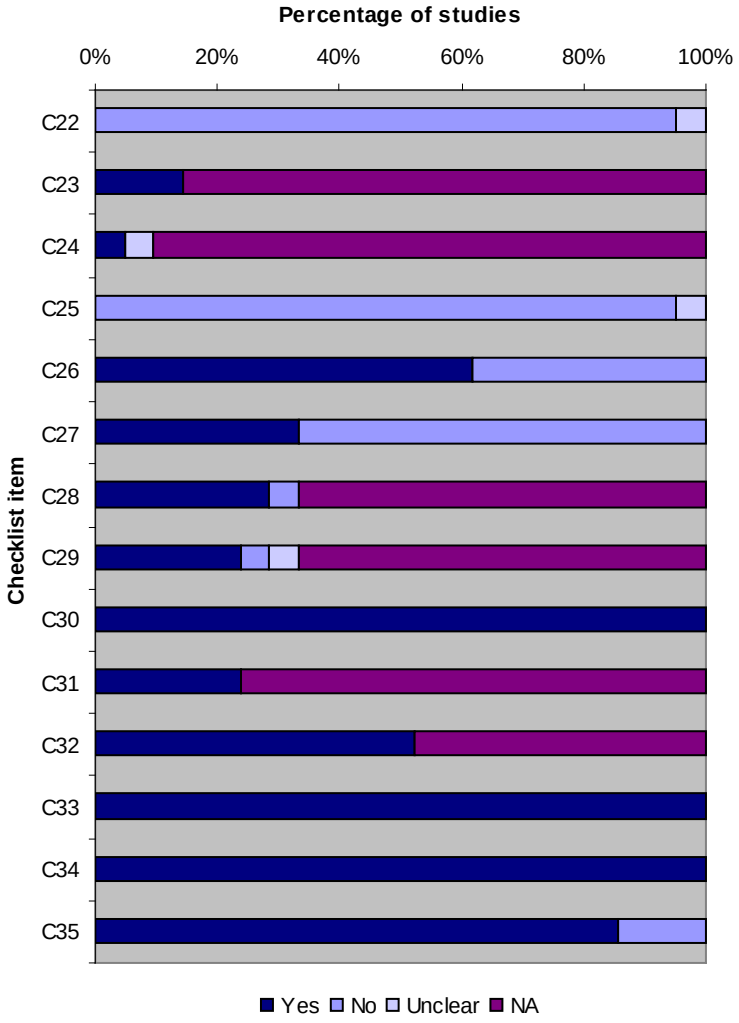


Checklist item	Quality statement
B8	The source(s) of effectiveness estimates used are stated.
B9	Details of the design and results of effectiveness study are given
B10	Details of the methods of synthesis or meta-analysis of estimates are given
B11	The primary outcome measure(s) for the economic evaluation are clearly stated.
B12	Methods to value benefits are stated.
B13	Details of the subjects from whom valuations were obtained were given.
B14	Productivity changes (if included) are reported separately.
B15	The relevance of productivity changes to the study question is discussed.
B16	Quantities of resource use are reported separately from their unit costs.
B17	Methods for the estimation of quantities and unit costs are described.
B18	Currency and price data are recorded.
B19	Details of currency of price adjustments for inflation or currency conversion are given.
B20	Details of any model used are given.
B21	The choice of model used and the key parameters on which it is based are justified.

Key findings (n=21):

- Benefits such as quality of life were not valued in any of the studies
- Resource use was reported separately to unit costs in 9 studies
- None of the studies developed an economic model

Appendix 22 Quality assessment – interpretation of results



Checklist item	Quality statement
C22	Time horizon of costs and benefits is stated.
C23	The discount rate(s) is stated.
C24	The choice of discount rate(s) is justified.
C25	An explanation is given if costs and benefits are not discounted.
C26	Details of statistical tests and CIs are given for data.
C27	The approach to sensitivity analysis is given.
C28	The choice of variables for sensitivity analysis is justified.
C29	The ranges over which the variables are varied are justified.
C30	Relevant alternatives are compared.
C31	Incremental analysis is reported.
C32	Major outcomes are presented in a disaggregated as well as aggregated form
C33	The answer to the study question is given.
C34	Conclusions follow from the data reported.
C35	Conclusions are accompanied by the appropriate caveats.

Key findings (n=21):

- The approach to sensitivity analysis was given in all 7 studies
- Incremental analysis was conducted in 5 studies

References

1. Addo J, Ayerbe L, Mohan KM, Crichton S, Sheldenkar A, Chen R, et al. Socioeconomic status and stroke: an updated review. Stroke 2012;43(4):1186-91.

2. National Health Service Quality Improvement Scotland. Scottish Intercollegiate Guidelines Network. Management of patients with stroke: Rehabilitation, prevention and management of complications, and discharge planning. 2010. ISBN 978 1 905813 63 6. Available from: www.sign.ac.uk.

3. Bernhardt J. Very early mobilization following acute stroke: Controversies, the unknowns, and a way forward. Annals of Indian Academy of Neurology 2008;11(5):88-98.

4. Bernhardt J, Dewey H, Collier J, Thrift A, Lindley R, Moodie M, et al. A Very Early Rehabilitation Trial (AVERT). Int J Stroke 2006;1(3):169-71.

5. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008;337:a1655.

6. The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. J Clin Epidemiol 1988;41(2):105-14.

7. Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. Lancet Neurol 2007;6(2):182-7.

8. World Health Organisation. International Classification of Functioning, Disability and Health (ICF). 2001. Available from: http://www.who.int.

9. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3(11):e442. doi:10.1371/journal.pmed.0030442.

10. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. Heart disease and stroke statistics-2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008;117(4):e25-146. doi: 10.1161/CIRCULATIONAHA.107.187998.

11. British Heart Foundation Health Promotion Research Group.European cardiovascular disease statistics. European Heart Network. 2008. Available from: http://www.ehnheart.org.

12. Saka O, McGuire A, Wolfe C. Cost of stroke in the United Kingdom. Age Ageing 2009;38(1):27-32.

13. Langhorne P, Legg L. Evidence behind stroke rehabilitation. J Neurol Neurosurg Psychiatry 2003;74 Suppl 4:iv18-iv21.

14. Stroke Unit Trialists' Collaboration Collaborative systematic review of the randomised trials of organised inpatient (stroke unit) care after stroke. BMJ 1997;314(7088):1151-9.

15. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. Cochrane Database of Systematic Reviews 2001,Issue 3. Art. No.: CD000197. DOI: 10.1002/14651858.CD000197.

16. Department of Health. National Stroke Strategy. 2007. Available from: www.dh.gov.uk/publications.

17. National Institute for Health and Clinical Excellence. Diagnosis and inital management of acute stroke and transient ischaemic attack (TIA). Royal College of Physicians. 2008. Available from: http://www.rcplondon.ac.uk.

18. Wade D T. Measurement in neurological rehabilitation. University Press; 1992.

19. Wade DT. Stroke: rehabilitation and long-term care. Lancet 1992;339(8796):791-3.

20. Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. Lancet 2011;377(9778):1693-702.

21. Kwakkel G, Kollen B, Lindeman E. Understanding the pattern of functional recovery after stroke: facts and theories. Restor Neurol Neurosci 2004;22(3-5):281-99.

22. Skilbeck CE, Wade DT, Hewer RL, Wood VA. Recovery after stroke. J Neurol Neurosurg Psychiatry 1983;46(1):5-8.

23. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke.[see comment][update of Cochrane Database Syst Rev. 2002;(1):CD000197; PMID: 11869570]. Cochrane Database of Systematic Reviews 2007(4):CD000197.

24. Ali M, Ashburn A, Bowen A, Brodie E, Corr S, Drummond A, et al. VISTA-Rehab: A resource for stroke rehabilitation trials. International Journal of Stroke 2010;5(6):447-52.

25. Brady MC, Stott DJ, Norrie J, Chalmers C, St George B, Sweeney PM, et al. Developing and evaluating the implementation of a complex intervention: using mixed methods to inform the design of a randomised controlled trial of an oral healthcare intervention after stroke. Trials;12:168.

26. Medical Research Council. A framework for development and evaluation of RCTs for Complex Interventions to improve Health. 2000. Available from: http://www.mrc.ac.uk.

27. Bernhardt J, Chitravas N, Meslo IL, Thrift AG, Indredavik B. Not all stroke units are the same: a comparison of physical activity patterns in Melbourne, Australia, and Trondheim, Norway. Stroke 2008;39(7):2059-65.

28. Wade DT, Smeets RJ, Verbunt JA. Research in rehabilitation medicine: methodological challenges. J Clin Epidemiol 2010;63(7):699-704.

29. Hawe P, Shiell A, Riley T. Complex interventions: how "out of control" can a randomised controlled trial be? BMJ 2004;328(7455):1561-3.

30. Oakley A, Strange V, Bonell C, Allen E, Stephenson J. Process evaluation in randomised controlled trials of complex interventions. BMJ 2006;332(7538):413-6.

31. May C, Finch T, Mair F, Ballini L, Dowrick C, Eccles M, et al. Understanding the implementation of complex interventions in health care: the normalization process model. BMC Health Serv Res 2007;7:148.

32. Campbell M, Fitzpatrick R, Haines A, Kinmonth A, Sandercock P, Spiegelhalter D, et al. Framework for design and evaluation of complex interventions to improve health. BMJ 2000;321(7262):694 - 96.

33. Davis DA, Taylor-Vaisey A. Translating guidelines into practice. A systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. CMAJ 1997;157(4):408-16.

34. Eccles MP, Hrisos S, Francis J, Kaner EF, Dickinson HO, Beyer F, et al. Do self- reported intentions predict clinicians' behaviour: a systematic review. Implement Sci 2006;1:28.

35. Titler MG. Methods in translation science. Worldviews Evid Based Nurs 2004;1(1):38-48.

36. Grol R, Wensing M, Eccles M (editors). Improving patient care: the implementation of change in clinical practice: a model. London: Elsevier;2005.

37. Hawe P, Shiell A, Riley T, Gold L. Methods for exploring implementation variation and local context within a cluster randomised community intervention trial. J Epidemiol Community Health 2004;58(9):788-93.

38. Baker R, Camosso-Stefinovic J, Gillies C, Shaw EJ, Cheater F, Flottorp S, Robertson N. Tailored interventions to overcome identified barriers to change:

effects on professional practice and health care outcomes. Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No.: CD005470. DOI: 10.1002/14651858.CD005470.pub2.

39. Hakkennes S, Dodd K. Guideline implementation in allied health professions: a systematic review of the literature. Qual Saf Health Care 2008;17(4):296-300.

40. Bonetti D, Eccles M, Johnston M, Steen N, Grimshaw J, Baker R, et al. Guiding the design and selection of interventions to influence the implementation of evidence-based practice: an experimental simulation of a complex intervention trial. Soc Sci Med 2005;60(9):2135-47.

41. Durlak JA, DuPre EP. Implementation matters: a review of research on the influence of implementation on program outcomes and the factors affecting implementation. Am J Community Psychol 2008;41(3-4):327-50.

42. Adams HP, Jr., Adams RJ, Brott T, del Zoppo GJ, Furlan A, Goldstein LB, et al. Guidelines for the Early Management of Patients With Ischemic Stroke: A Scientific Statement From the Stroke Council of the American Stroke Association. Stroke 2003;34(4):1056-83.

43. Australian Government. Clinical guidelines for acute stroke management - National Stroke Foundation. 2007. Available from: www.strokefoundation.com.au.

44. Wojner AW, El-Mitwalli A, Alexandrov AV. Effect of head positioning on intracranial blood flow velocities in acute ischemic stroke: a pilot study. Crit Care Nurs Q 2002;24(4):57-66.

45. Bernhardt J, Dewey H, Thrift A, Collier J, Donnan G. A very early rehabilitation trial for stroke (AVERT): phase II safety and feasibility. Stroke 2008;39(2):390-6.

46. Bernhardt J, Dewey H, Thrift A, Donnan G. Inactive and alone: physical activity within the first 14 days of acute stroke unit care. Stroke

2004;35(4):1005-9.

47. Indredavik B, Bakke F, Solberg R, Rokseth R, Haaheim LL, Holme I. Benefit of a stroke unit: a randomized controlled trial. Stroke 1991;22(8):1026-31.

48. Partridge CJ, Morris LW, Edwards MS. Recovery from physical disability after stroke: profiles for different levels of starting severity. Clinical Rehabilitation 1993;7(3):210-17.

49. Paolucci S, Bragoni M, Coiro P, De Angelis D, Fusco FR, Morelli D, et al. Quantification of the probability of reaching mobility independence at discharge from a rehabilitation hospital in nonwalking early ischemic stroke patients: A multivariate study. Cerebrovascular Diseases 2008;26(1):16-22.

50. Suzuki K, Imada G, Iwaya T, Handa T, Kurogo H. Determinants and predictors of the maximum walking speed during computer-assisted gait training in hemiparetic stroke patients. Archives of Physical Medicine and Rehabilitation 1999;80(2):179-82.

51. Counsell C, Dennis M. Systematic review of prognostic models in patients with acute stroke. Cerebrovasc Dis 2001;12(3):159-70.

52. Bussmann JB, Stam HJ. Techniques for measurement and assessment of mobility in rehabilitation: a theoretical approach. Clin Rehabil 1998;12(6):455-64.

53. Hendricks H, Zwarts M, Plat E, Van LJ. Systematic review for the early prediction of motor and functional outcome after stroke by using motor-evoked potentials. Archives of Physical Medicine and Rehabilitation 2002;83(9):1303-8.

54. Jongbloed L. Prediction of function after stroke: A critical review. Stroke 1986;17(4):765-76.

55. Kwakkel G, Wagenaar RC, Kollen BJ, Lankhorst GJ. Predicting disability in stroke - A critical review of the literature. Age and Ageing 1996;25(6):479-89.

56. Nitz J, Gage A. Post stroke recovery of balanced sitting and ambulation ability. Australian Journal of Physiotherapy 1995;41(4):263-7.

57. Van dPI, Kwakkel G, Schepers V, Lindeman E. Predicting mobility outcome one year after stroke: a prospective cohort study. Journal of Rehabilitation Medicine 2006;38(4):218-23.

58. Pettersen R, Dahl T, Wyller T. Prediction of long-term functional outcome after stroke rehabilitation. Clinical Rehabilitation 2002;16(2):149-59.

59. Sanchez-Blanco I, Ochoa-Sangrador C, Lopez-Munain L, Izquierdo-Sanchez M, Fermoso-Garcia J. Predictive model of functional independence in stroke patients admitted to a rehabilitation programme. Clinical Rehabilitation 1999;13(6):464-75.

60. Meijer R, Ihnenfeldt D, de GI, van LJ, Vermeulen M, de HR. Prognostic factors for ambulation and activities of daily living in the subacute phase after stroke. A systematic review of the literature. Clin Rehabil 2003;17(2):119-29.

61. Pearson OR, Busse ME, van Deursen RW, Wiles CM. Quantification of walking mobility in neurological disorders. QJM 2004;97(8):463-75.

62. Hendricks H, Zwarts M, Plat E, Van LJ. Systematic review for the early prediction of motor and functional outcome after stroke by using motor-evoked potentials. Archives of Physical Medicine and Rehabilitation 2002;83(9):1303-8.

63. Loewen SC, Anderson BA. Predictors of stroke outcome using objective measurement scales. Stroke 1990;21(1):78-81.

64. Singh R, Hunter J, Philip A, Todd I. Predicting those who will walk after rehabilitation in a specialist stroke unit. Clin Rehabil 2006;20(2):149-52.

65. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. Lancet Neurol 2009;8(8):741-54.

66. Ford AB, Katz S. Prognosis after strokes: a critical review. Medicine (Baltimore) 1966;45(3):223-46.

67. Gray CS, French JM, Bates D, Cartlidge NE, James OF, Venables G. Motor recovery following acute stroke. Age Ageing 1990;19(3):179-84.

68. Partridge CJ, Morris L. Recovery from physical disability after stroke: profiles for different levels of starting severity. Clinical Rehabilitation 1993;7(3):210-17.

69. Symposium Recommendations for Methodology in Stroke Outcome Research: Task Force on Stroke Impairment, Task Force on Stroke Disability, and Task Force on Stroke Handicap. Stroke 1990;21(9) Supplement(II):II-68-II-73.

70. Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. BMJ 2009;338:b605. doi: 10.1136/bmj.b605.

71. Moons KG, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. BMJ 2009;338:b606. doi: 10.1136/bmj.b606

72. Royston P, Moons KG, Altman DG, Vergouwe Y. Prognosis and prognostic research: Developing a prognostic model. BMJ 2009;338:b604. doi: 10.1136/bmj.b604

73. Aarabi B, Taghipour M, Haghnegahdar A, Farokhi M, Mobley L. Prognostic factors in the occurrence of posttraumatic epilepsy after penetrating head injury suffered during military service. Neurosurgical Focus 2000;8(1):1-6.

74. Baer G, Smith M. The recovery of walking ability and subclassification of stroke. Physiotherapy Research International 2001;6(3):135-44.

75. Friedman P. Gait recovery after hemiplegic stroke. Int Disabil Stud 1990;12(3):119-22.

76. Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Recovery of walking function in stroke patients: the Copenhagen Stroke Study. Archives of Physical Medicine & Rehabilitation 1995;76(1):27-32.

77. Matsunaga A, Kurokawa Y, Kanda T, Sakai F. Prediction of locomotion function at one month after stroke. Journal of Physical Therapy Science 1997;9(2):93-7.

78. Smith M, Baer G. Achievement of simple mobility milestones after stroke. Archives of Physical Medicine and Rehabilitation 1999;80(4):442-7.

79. Reeves RA, Leenen FH, Joyner CD. Reproducibility of nurse-measured, exercise and ambulatory blood pressure and echocardiographic left ventricular mass in borderline hypertension. J Hypertens 1992;10(10):1249-56.

80. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15(4):361-87.

81. Taylor JMG, Yu M. Bias and Efficiency Loss Due to Categorizing an Explanatory Variable. Journal of Multivariate Analysis 2002;83(1):248-63.

82. Altman DG. Categorising continuous variables. Br J Cancer 1991;64(5):975-75.

83. Hosmer DW, Leseshow S. Applied Logistic Regression. 2nd ed. New Jersey: Wiley-Interscience; 2000.

84. Lewis SC, Sandercock PA, Dennis MS. Predicting outcome in hyper-acute stroke: validation of a prognostic model in the Third International Stroke Trial (IST3). J Neurol Neurosurg Psychiatry 2008;79(4):397-400.

85. Mayo NE, Kornerbitensky NA, Becker R. Recovery-time of independent function poststroke. American Journal of Physical Medicine & Rehabilitation 1991;70(1):5-12.

86. Bagg S, Pombo AP, Hopman W. Effect of age on functional outcomes after stroke rehabilitation. Stroke 2002;33(1):179-85.

87. Barer DH. Continence after stroke: Useful predictor or goal of therapy. Age and Ageing 1989;18(3):183-91.

88. Bohannon RW. Gait performance of hemiparetic stroke patients: Selected variables. Archives of Physical Medicine and Rehabilitation 1987;68(11):777-81.

89. Brun V, Labauge P, Robinson A, Benaim C, Dhoms G, Torres B, et al. Factors affecting gait recovery after hemiplegic stroke. [French]. Annales de Readaptation et de Medecine Physique 1996;39(4):191-99.

90. Singh R, Hunter J, Philip A, Todd I. Predicting those who will walk after rehabilitation in a specialist stroke unit. Clinical Rehabilitation 2006;20(2):149-52.

91. Smith J, Brotheridge S, Young J. Patterns of hemiparesis recovery in lacunar and partial anterior circulation infarct stroke syndromes. Clinical Rehabilitation 2001;15(1):59-66.

92. Partridge C, Edwards S. Recovery Curves as a Basis for Evaluation. Physiotherapy 1988;74(3):141-43.

93. Veerbeek JM, Van Wegen EE, Harmeling-Van der Wel BC, Kwakkel G. Is accurate prediction of gait in nonambulatory stroke patients possible within 72 hours poststroke? The EPOS study. Neurorehabil Neural Repair 2011;25(3):268-

94. Stinear C. Prediction of recovery of motor function after stroke. The Lancet Neurology. 2010;9(12): 1228-1232.

95. Dallas MI, Rone-Adams S, Echternach JL, Brass LM, Bravata DM. Dependence in prestroke mobility predicts adverse outcomes among patients with acute ischemic stroke. Stroke 2008;39(8):2298-303.

96. Bamford J, Dennis M, Sandercock P, Burn J, Warlow C. The frequency, causes and timing of death within 30 days of a first stroke: the Oxfordshire Community Stroke Project. J Neurol Neurosurg Psychiatry 1990;53(10):824-9.

97. Masiero S, Avesani R, Armani M, Verena P, Ermani M. Predictive factors for ambulation in stroke patients in the rehabilitation setting: A multivariate analysis. Clinical Neurology and Neurosurgery 2007;109(9):763-69.

98. Altman DG. Systematic reviews of evaluations of prognostic variables. BMJ 2001;323(7306):224-8.

99. Riley RD, Ridley G, Williams K, Altman DG, Hayden J, de Vet HC. Prognosis research: toward evidence-based results and a Cochrane methods group. J Clin Epidemiol 2007;60(8):863-5; author reply 65-6.

100. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep 1985;100(2):126-31.

101. Indredavik B, Bakke F, Slordahl SA, Rokseth R, Haheim LL. Treatment in a combined acute and rehabilitation stroke unit: which aspects are most important? Stroke 1999;30(5):917-23.

102. Langhorne P, Wagenaar R, Partridge C. Physiotherapy after stroke: more is better? Physiother Res Int 1996;1(2):75-88.

103. Keith RA. Activity patterns of a stroke rehabilitation unit. Soc Sci Med Med Psychol Med Sociol 1980;14A(6):575-80.

104. Keith RA, Cowell KS. Time use of stroke patients in three rehabilitation hospitals. Soc Sci Med 1987;24(6):529-33.

105. Lincoln NB, Willis D, Philips SA, Juby LC, Berman P. Comparison of rehabilitation practice on hospital wards for stroke patients. Stroke 1996;27(1):18-23.

106. Newall JT, Wood VA, Hewer RL, Tinson DJ. Development of a neurological rehabilitation environment: an observational study. Clin Rehabil 1997;11(2):146-55.

107. Wellwood I, Langhorne P, McKevitt C, Bernhardt J, Rudd AG, Wolfe CDA. An observational study of acute stroke care in four countries: the European registers of stroke study. Cerebrovascular Diseases 2009;28(2):171-6.

108. De Wit L, Putman K, Dejaeger E, Baert I, Berman P, Bogaerts K, et al. Use of time by stroke patients: a comparison of four European rehabilitation centers. Stroke 2005;36(9):1977-83.

109. Lincoln NB, Gamlen R, Thomason H. Behavioural mapping of patients on a stroke unit. Int Disabil Stud 1989;11(4):149-54.

110. Beech R, Ratcliffe M, Tilling K, Wolfe C. Hospital services for stroke care. A European Perspective. European Study of Stroke Care. Stroke 1996;27(11):1958-64.

111. Mackey F, Ada L, Heard R, Adams R. Stroke rehabilitation: are highly structured units more conducive to physical activity than less structured units? Arch Phys Med Rehabil 1996;77(10):1066-70.

112. Egerton T, Maxwell DJ, Granat MH. Mobility Activity of Stroke Patients During Inpatient Rehabilitation. Hong Kong Physiotherapy Journal 2006;24:8-15.

113. Pound P, Sabin C, Ebrahim S. Observing the process of care: a stroke unit, elderly care unit and general medical ward compared. Age Ageing 1999;28(5):433-40.

114. Hale LA, Pal J, Becker I. Measuring free-living physical activity in adults with and without neurologic dysfunction with a triaxial accelerometer. Arch Phys Med Rehabil 2008;89(9):1765-71.

115. Britton E, Harris N, Turton A. An exploratory randomized controlled trial of

assisted practice for improving sit-to-stand in stroke patients in the hospital setting. Clin Rehabil 2008;22(5):458-68.

116. The Glasgow Augmented Physiotherapy Study (GAPS) group. Can augmented physiotherapy input enhance recovery of mobility after stroke? A randomized controlled trial. Clin Rehabil 2004;18(5):529-37.

117. Stamatakis E, Davis M, Stathi A, Hamer M. Associations between multiple indicators of objectively-measured and self-reported sedentary behaviour and cardiometabolic risk in older adults. Prev Med 2012;54(1):82-7.

118. Stamatakis E, Hamer M, Dunstan DW. Screen-based entertainment time, all-cause mortality, and cardiovascular events: population-based study with ongoing mortality and hospital events follow-up. J Am Coll Cardiol 2011;57(3):292-9.

119. Healy GN, Dunstan DW, Salmon J, Cerin E, Shaw JE, Zimmet PZ, et al. Breaks in sedentary time: beneficial associations with metabolic risk. Diabetes Care 2008;31(4):661-6.

120. English C. Was the effect of sitting time interpreted appropriately? J Physiother 2011;57(2):132; author reply 33.

121. Rand D, Eng JJ, Tang PF, Jeng JS, Hung C. How active are people with stroke?: use of accelerometers to assess physical activity. Stroke 2009;40(1):163-8.

122. Godfrey A, Culhane KM, Lyons GM. Comparison of the performance of the activPAL Professional physical activity logger to a discrete accelerometer-based activity monitor. Med Eng Phys 2007;29(8):930-4.

123. Grant PM, Ryan CG, Tigbe WW, Granat MH. The validation of a novel activity monitor in the measurement of posture and motion during everyday activities. Br J Sports Med 2006;40(12):992-97.

124. Ryan CG, Grant PM, Tigbe WW, Granat MH. The validity and reliability of a

novel activity monitor as a measure of walking. Br J Sports Med 2006;40(9):779-84.

125. Ryan CG, Grant PM, Gray H, Newton M, Granat MH. Measuring postural physical activity in people with chronic low back pain. Journal of Back & Musculoskeletal Rehabilitation 2008;21(1):43-50.

126. Gebruers N, Vanroy C, Truijen S, Engelborghs S, De Deyn PP. Monitoring of Physical Activity After Stroke: A Systematic Review of Accelerometry-Based Measures. Arch Phys Med Rehabil 2010;91(2):288-97.

127. A Very Early Rehabilitation Trialists. Contamination of Standard Care:A Substudy of AVERT - A Very Early Rehabilitation Trial. 2009;Protocol Version 1.2 – 24 April 2009. Available from: http://www.florey.edu.au/research/stroke/a-very-early-rehabilitation-trial-avert-phase-iii.

128. West T, Bernhardt J. Physical activity in hospitalised stroke patients. Stroke Res Treat 2012;2012:813765.

129. Della Pietra GL, Savio K, Oddone E, Reggiani M, Monaco F, Leone MA. Validity and reliability of the Barthel index administered by telephone. Stroke 2011;42(7):2077-9.

130. Grant PM, Granat MH, Thow MK, Maclaren WM. Analyzing free-living physical activity of older adults in different environments using body-worn activity monitors. J Aging Phys Act 2010;18(2):171-84.

131. Bagley P, Hudson M, Green J, Forster A, Young J. Do physiotherapy staff record treatment time accurately? An observational study. Clin Rehabil 2009;23(9):841-5.

132. Bland JM, Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res 1999;8(2):135-60.

133. Taraldsen K, Askim T, Sletvold O, Einarsen EK, Bjastad KG, Indredavik B, et

al. Evaluation of a body-worn sensor system to measure physical activity in older people with impaired function. Phys Ther 2011;91(2):277-85.

134. Harris TJ, Owen CG, Victor CR, Adams R, Cook DG. What factors are associated with physical activity in older people, assessed objectively by accelerometry? Br J Sports Med 2009;43(6):442-50.

135. Askim T, Bernhardt J, Salvesen Ø, Indredavik B. Increased amount of physical activity in the acute phase is associated with good functional outcome 3 months after stroke. 2012.Abstract presented at European Stroke Conference, Lisbon. Available from: http://www.esc-archive.eu.

136. Pickering RM, Kunkel D, Fitton C, Ashburn A, Jenkinson D. In-hospital recruitment to observational studies of stroke. Int J Rehabil Res 2010;33(1):56-63.

137. Sedentary Behaviour Research N. Letter to the editor: standardized use of the terms "sedentary" and "sedentary behaviours". Appl Physiol Nutr Metab 2012;37(3):540-5.

138. Ward DS, Evenson KR, Vaughn A, Rodgers AB, Troiano RP. Accelerometer use in physical activity: best practices and research recommendations. Med Sci Sports Exerc 2005;37(11 Suppl):S582-8.

139. King AC, Ahn DK, Oliveira BM, Atienza AA, Castro CM, Gardner CD. Promoting physical activity through hand-held computer technology. Am J Prev Med 2008;34(2):138-42.

140. Glass G. Primary, secondary and meta-analysis of research. Educ Res 1976;5:3-8.

141. Langhorne P, Stott D, Knight A, Bernhardt J, Barer D, Watkins C. Very early rehabilitation or intensive telemetry after stroke: a pilot randomised trial. Cerebrovasc Dis 2010;29(4):352-60.

142. Bernhardt J, Thuy MNT, Collier JM, Legg LA. Very early versus delayed mobilisation after stroke. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD006187. DOI: 10.1002/14651858.CD006187.pub2.

143. Lyden P, Lu M, Jackson C, Marler J, Kothari R, Brott T, et al. Underlying structure of the National Institutes of Health Stroke Scale: results of a factor analysis. NINDS tPA Stroke Trial Investigators. Stroke 1999;30(11):2347-54.

144. Scandinavian Stroke Study Group. Multicenter trial of hemodilution in ischemic stroke--background and study protocol. Stroke 1985;16(5):885-90.

145. Gray LJ, Ali M, Lyden PD, Bath PMW. Interconversion of the National Institutes of Health Stroke Scale and Scandinavian Stroke Scale in Acute Stroke. Journal of Stroke and Cerebrovascular Diseases 2009;18(6):466-68.

146. Borg G. Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med 1970;2(2):92-8.

147. Collen FM, Wade DT, Robb GF, Bradshaw CM. The Rivermead Mobility Index: a further development of the Rivermead Motor Assessment. Int Disabil Stud 1991;13(2):50-4.

148. Hawthorne G. The Australian Multi-attribute Utility (AMAU): Construction and Initial Evaluation. 1996. Available from: http://www.buseco.monash.edu.au

149. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

150. Tay-Teo K, Moodie M, Bernhardt J, Thrift AG, Collier J, Donnan G, et al. Economic evaluation alongside a phase II, multi-centre, randomised controlled trial of very early rehabilitation after stroke (AVERT). Cerebrovasc Dis 2008;26(5):475-81.

151. Donabedian A. The quality of care. How can it be assessed? JAMA

1988;260(12):1743-8.

152. Wilcoxon F. Individual comparisons by ranking methods. Biometrics 1945;1:80-83.

153. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7(3):177-88.

154. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557-60.

155. Simmonds MC, Higgins JP, Stewart LA, Tierney JF, Clarke MJ, Thompson SG. Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. Clin Trials 2005;2(3):209-17.

156. Musicco M, Emberti L, Nappi G, Caltagirone C. Early and long-term outcome of rehabilitation in stroke patients: the role of patient characteristics, time of initiation, and duration of interventions. Arch Phys Med Rehabil 2003;84(4):551-8.

157. Adams HP, Jr., Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Neurology 1999;53(1):126-31.

158. Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ 2006;332(7549):1080.

159. Paolucci S, Antonucci G, Grasso MG, Morelli D, Troisi E, Coiro P, et al. Early versus delayed inpatient stroke rehabilitation: a matched comparison conducted in Italy. Arch Phys Med Rehabil 2000;81(6):695-700.

160. Salter K, Jutai J, Hartley M, Foley N, Bhogal S, Bayona N, et al. Impact of early vs delayed admission to rehabilitation on functional outcomes in persons with stroke. J Rehabil Med 2006;38(2):113-7.

161. Dechartres A, Boutron I, Trinquart L, Charles P, Ravaud P. Single-center trials show larger treatment effects than multicenter trials: evidence from a meta-epidemiologic study. Ann Intern Med 2011;155(1):39-51.

162. Diserens K, Moreira T, Hirt L, Faouzi M, Grujic J, Bieler G, et al. Early mobilization out of bed after ischaemic stroke reduces severe complications but not cerebral blood flow: a randomized controlled pilot trial. Clin Rehabil 2012;26(5):451-9.

163. Cumming TB, Thrift AG, Collier JM, Churilov L, Dewey HM, Donnan GA, et al. Very early mobilization after stroke fast-tracks return to walking: further results from the phase II AVERT randomized controlled trial. Stroke 2011;42(1):153-8.

164. Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference? Lancet 1993;341(8842):418-22.

165. Oxman AD, Guyatt GH. A consumer's guide to subgroup analyses. Ann Intern Med 1992;116(1):78-84.

166. Redfern J, McKevitt C, Wolfe CD. Development of complex interventions in stroke care: a systematic review. Stroke 2006;37(9):2410-9.

167. Thomson R. Evidence based implementation of complex interventions. BMJ 2009;339:b3124.

168. Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. Health Technol Assess 2004;8(6):iii-iv, 1-72.

169. Greenhalgh T, Robert G, Macfarlane F, Bate P, Kyriakidou O. Diffusion of innovations in service organizations: systematic review and recommendations. Milbank Q 2004;82(4):581-629.

170. Power ML, Cross SP, Roberts S, Tyrrell PJ. Evaluation of a service

development to implement the top three process indicators for quality stroke care. J Eval Clin Pract 2007;13(1):90-4.

171. Lewin S, Glenton C, Oxman AD. Use of qualitative methods alongside randomised controlled trials of complex healthcare interventions: methodological study. BMJ 2009;339:b3496. doi: 10.1136/bmj.b3496.

172. Robben SH, Perry M, Huisjes M, van Nieuwenhuijzen L, Schers HJ, van Weel C, et al. Implementation of an innovative web-based conference table for community-dwelling frail older people, their informal caregivers and professionals: a process evaluation. BMC Health Serv Res 2012;12(1):251.

173. Flottorp S, Havelsrud K, Oxman AD. Process evaluation of a cluster randomized trial of tailored interventions to implement guidelines in primary care-why is it so hard to change practice? Fam Pract 2003;20(3):333-9.

174. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet 2003;362(9391):1225-30.

175. Scott SD, Osmond MH, O'Leary KA, Graham ID, Grimshaw J, Klassen T. Barriers and supports to implementation of MDI/spacer use in nine Canadian pediatric emergency departments: a qualitative study. Implement Sci 2009;4(1):65.

176. Barte JC, Ter Bogt NC, Beltman FW, van der Meer K, Bemelmans WJ. Process Evaluation of a Lifestyle Intervention in Primary Care: Implementation Issues and the Participants' Satisfaction of the GOAL Study. Health Educ Behav 2011;39(5):564-73.

177. Chen HT, Grimley DM, Waithaka Y, Aban IB, Hu J, Bachmann LH. A process evaluation of the implementation of a computer-based, health provider-delivered HIV-prevention intervention for HIV-positive men who have sex with men in the primary care setting. AIDS Care 2008;20(1):51-60.

178. Arias M, Smith LN. Early mobilization of acute stroke patients. J Clin Nurs

2007;16(2):282-8.

179. Skarin M, Bernhardt J, Sjoholm A, Nilsson M, Linden T. 'Better wear out sheets than shoes': a survey of 202 stroke professionals' early mobilisation practices and concerns. Int J Stroke 2011;6(1):10-5.

180. Sjoholm A, Skarin M, Linden T, Bernhardt J. Does evidence really matter? Professionals' opinions on the practice of early mobilization after stroke. J Multidiscip Healthc 2011;4:367-76.

181. Forgas JP. Belief and affect: On the mental pre-cursors of health-related cognition and behaviour. J Health Psychol 2012.

182. Patton MQ. Qualitative Research and Evaluation Methods.3rd ed.London:Sage Publications; 2002.

183. Morgan DL. The focus group guide book.London:Sage Publications;1998.

184. Fontana A and Frey J. The interview. In: Denzin N, Lincoln Y, editors. The Sage Handbook of Qualitative Research. London. Sage publications; 2000.

185. Mason J. Qualitative Researching.2nd ed.London:Sage Publications;2002

186. Cadilhac DA, Ibrahim J, Pearce DC, Ogden KJ, McNeill J, Davis SM, et al. Multicenter Comparison of Processes of Care Between Stroke Units and Conventional Care Wards in Australia. Stroke 2004;35(5):1035-40.

187. Robson C. Real World Research.2nd ed.London: Blackwell Publishers;2002.

188. Strauss AL, Corbin J. Basics of Qualitative: Grounded Theory Procedures and Techniques. 2nd ed.London:Sage Publications;1998.

189. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology 2006;3(2):77-101.

190. Ritchie J, Lewis J. Qualitative Research Practice: A Guide for Social Science

Students and Researchers. London: Sage Publications; 2007.

191. Flick U. An Introduction to Qualitative Research. London: Sage Publications;1998.

192. Taylor SJ, Bogdan R. Introduction to qualitative research methods: The search for meanings.New York:John Wiley;1984.

193. Evenson KR, Rosamond WD, Vallee JA, Morris DL. Concordance of stroke symptom onset time. The Second Delay in Accessing Stroke Healthcare (DASH II) Study. Ann Epidemiol 2001;11(3):202-7.

194. NHS Institute for Innovation and Improvement. Improving healthcare quality at scale and Lessons from the Productive Ward: Releasing time to care. Last accessed at http://www.institute.nhs.uk/quality_and_value/productivity_series/productive_ward.html, August 2012.

195. Horgan NF, Finn AM. Motor recovery following stroke: a basis for evaluation. Disabil Rehabil 1997;19(2):64-70.

196. May C. A rational model for assessing and evaluating complex interventions in health care. BMC Health Serv Res 2006;6:86.

197. Rogers EM. Diffusion of innovations. 4th ed. New York: Free Press; 2003.

198. Kitson A, Harvey G, McCormack B. Enabling the implementation of evidence based practice: a conceptual framework. Qual Health Care 1998;7(3):149-58.

199. Herron J. The facilitator's handbook. 4th ed. London: Kogan Page Limited; 1989.

200. Greenwood CR, Tapia Y, Abbott M, Walton C. A Building-Based Case Study of Evidence-Based Literacy Practices. The Journal of Special Education 2003;37(2):95-110.

201. Gray GR. Quality Circles: An Update. SAM Advanced Management Journal (07497075) 1993;58(2):41.

202. Evers SM, Ament AJ, Blaauw G. Economic evaluation in stroke research: a systematic review. Stroke 2000;31(5):1046-53.

203. Guilhaume C, Saragoussi D, Cochran J, François C, Toumi M. Modeling stroke management: a qualitative review of cost-effectiveness analyses. The European Journal of Health Economics 2010;11(4):419-26.

204. Holloway RG, Benesch CG, Rahilly CR, Courtright CE. A systematic review of cost-effectiveness research of stroke evaluation and treatment. Stroke 1999;30(7):1340-9.

205. Brady BK, McGahan L, Skidmore B. Systematic review of economic evidence on stroke rehabilitation services. Int J Technol Assess Health Care 2005;21(1):15-21.

206. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. BMJ 1996;313(7052):275-83.

207. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess 2004;8(36):iii-iv, ix-xi, 1-158.

208. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for Economic Evaluation of Health Care Programmes. London: Oxford University Press; 1997.

209. National Institute for Health and Clinical Excellence (NICE) London: NICE; 2008. Guide to the Methods of Technology Appraisal. http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf. Accessed February 2012.

210. Measuring effectiveness and cost effectiveness: the QALY. Last accessed at http://www.nice.org.uk/newsroom/features/measuringeffectivenessandcosteff

ectivenesstheqaly.jsp, August 2012.

211. Anderson C, Mhurchu CN, Rubenach S, Clark M, Spencer C, Winsor A. Home or hospital for stroke rehabilitation? Results of a randomized controlled trial. II: Cost minimization analysis at 6 months. Stroke 2000;31 (5):1032-37.

212. Beech R, Rudd AG, Tilling K, Wolfe CD. Economic consequences of early inpatient discharge to community-based rehabilitation for stroke in an inner-London teaching hospital. Stroke;30(4):729-35 1999.

213. Bjorkdahl A, Nilsson AL, Grimby G, Sunnerhagen KS. Does a short period of rehabilitation in the home setting facilitate functioning after stroke? A randomized controlled trial. Clinical Rehabilitation 2006;20 (12):1038-49.

214. Chen WH, Yu B, Xie XH, Tu XF. Application and cost-effectiveness analysis of three-stage rehabilitation program in treating acute stroke. Chinese Journal of Clinical Rehabilitation 2006;10 (48):31-33.

215. Donnelly M, Power M, Russell M, Fullerton K. Randomized Controlled Trial of an Early Discharge Rehabilitation Service: The Belfast Community Stroke Trial. Stroke 2004;35 (1):127-33.

216. Gladman J, Whynes D, Lincoln N. Cost comparison of domiciliary and hospital-based stroke rehabilitation. Age and Ageing 1994;23 (3):241-45.

217. Harrington R, Taylor G, Hollinghurst S, Reed M, Kay H, Wood VA. A community-based exercise and education scheme for stroke survivors: a randomized controlled trial and economic evaluation. Clinical Rehabilitation 2010;24 (1):3-15.

218. Huijbregts MP, Myers AM, Streiner D, Teasell R. Implementation, process, and preliminary outcome evaluation of two community programs for persons with stroke and their care partners. Topics in Stroke Rehabilitation 2008;15(5):503-20.

219. Keith RA, Wilson DB, Gutierrez P. Acute and subacute rehabilitation for stroke: a comparison. Archives of Physical Medicine & Rehabilitation. 1995; 76(6):495-500.

220. Larsen T, Olsen TS, Sorensen J. Early home-supported discharge of stroke patients: A health technology assessment. International Journal of Technology Assessment in Health Care 2006;22(3):313-20.

221. Mcnamee P, Christensen J, Soutter J, Rodgers H, Craig N, Pearson P, et al. Cost analysis of early supported hospital discharge for stroke. Age and Ageing 1998;27(3):345-51.

222. Roderick P, Low J, Day R, Peasgood T, Mullee MA, Turnbull JC, et al. Stroke rehabilitation after hospital discharge: A randomized trial comparing domiciliary and day-hospital care. Age and Ageing 2001;30(4):303-10.

223. Rodgers H, Mackintosh J, Price C, Wood R, McNamee P, Fearon T, et al. Does an early increased-intensity interdisciplinary upper limb therapy programme following acute stroke improve outcome? Clinical Rehabilitation 2003;17(6):579-89.

224. Sritipsukho P, Riewpaiboon A, Chaiyawat P, Kulkantrakorn K. Cost-effectiveness analysis of home rehabilitation programs for Thai stroke patients. Journal of the Medical Association of Thailand 2010;93 Suppl 7:S262-70.

225. Tay-Teo K, Moodie M, Bernhardt J, Thrift AG, Collier J, Donnan G, et al. Economic evaluation alongside a phase II, multi-centre, randomised controlled trial of very early rehabilitation after stroke (AVERT). Cerebrovascular Diseases 2008;26(5):475-81.

226. Teng J, Mayo NE, Latimer E, Hanley J, Wood-Dauphinee S, Cote R, et al. Costs and caregiver consequences of early supported discharge for stroke patients. Stroke 2003;34(2):528-36.

227. Von Koch L, De Pedro-Cuesta J, Kostulas V, Almazan J, Holmqvist LW.

Randomized controlled trial of rehabilitation at home after stroke: One-year follow-up of patient outcome, resource use and cost. Cerebrovascular Diseases 2001;12(2):131-38.

228. Widen HL, de Pedro CJ, Moller G, Holm M, Siden A. A pilot study of rehabilitation at home after stroke: a health-economic appraisal. Scandinavian Journal of Rehabilitation Medicine.28(1):9-18 1996.

229. Xiao WZ, Fan DS, Fu GM, Li J, Zhang XY, Sui W. The clinical economic evaluation of the early rehabilation treatment for the stroke patients. Chinese Journal of Clinical Rehabilitation 2004;8(10):1811-13.

230. Yagura H, Miyai I, Suzuki T, Yanagihara T. Patients with severe stroke benefit most by interdisciplinary rehabilitation team approach. Cerebrovascular Diseases 2005;20(4):258-63.

231. Young J, Forster A. Day hospital and home physiotherapy for stroke patients: a comparative cost-effectiveness study. Journal of the Royal College of Physicians of London 1993;27(3):252-58.

232. Barasa EW, English M. Viewpoint: Economic evaluation of package of care interventions employing clinical guidelines. Trop Med Int Health 2011;16(1):97-104.

233. Centre for Health Economics. Australia. Assessment of Quality of Life. Last accessed at http://www.aqol.com.au/scoring-algorithms.html, August 2012.

234. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Econ 2005;14(5):487-96.

235. Anderson R. Systematic reviews of economic evaluations: utility or futility? Health Econ 2010;19(3):350-64.

236. Tinson DJ. How stroke patients spend their days. An observational study of

the treatment regime offered to patients in hospital with movement disorders following stroke. Int Disabil Stud 1989;11(1):45-9.

237. NHS reference costs 2009/10: collection guidance. Last assessed at http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyndGuidance/DH_112590, August 2012.

238. NHS Information Centre for health and social care. Last accessed at www.ic.nhs.uk/casemix, August 2012.

239. Curtis L. Unit costs of health and social care. Personnel Social Services Unit 2009. Available from: http://www.pssru.ac.uk/archive.

240. Ramsey S, Willke R, Briggs A, Brown R, Buxton M, Chawla A, et al. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. Value Health 2005;8(5):521-33.

241. McGuire A. Theoretical concepts in the economic evaluation of healthcare. In: Drummond M, McGuire A, editors. Economic evaluation in health care: merging theory with practice. London: Oxford University Press; 2001.

242. Office of National Statistics. Annual Survey of Hours and Earnings. Statistics Bulletin. 2010. Available from http://www.ons.gov.uk/ons/index.html

243. Koopmanschap MA, van Exel JN, van den Berg B, Brouwer WB. An overview of methods and applications to value informal care in economic evaluations of healthcare. Pharmacoeconomics 2008;26(4):269-80.

244. Shepperd S, Lewin S, Straus S, Clarke M, Eccles MP, Fitzpatrick R, et al. Can we systematically review studies that evaluate complex interventions? PLoS Med 2009;6(8):e1000086. doi:10.1371/journal.pmed.1000086.

245. Lorgelly PK, Lawson KD, Fenwick EA, Briggs AH. Outcome measurement in economic evaluations of public health interventions: a role for the capability approach? Int J Environ Res Public Health 2010;7(5):2274-89.

246. Claxton K. Exploring uncertainty in cost-effectiveness analysis. Pharmacoeconomics 2008;26(9):781-98.

247. Davis JC, Robertson MC, Comans T, Scuffham PA. Guidelines for conducting and reporting economic evaluation of fall prevention strategies. Osteoporos Int 2011;22(9):2449-59.

248. Nobre FF, Trotta LT, Gomes LF. Multi-criteria decision making--an approach to setting priorities in health care. Stat Med 1999;18(23):3345-54.

249. Devlin N and Sussex J. Incorporating Multiple Criteria in HTA. Office of Health Economics; 2011.Available from http://www.ohe.org/page/index.cfm.

250. Goetghebeur MM, Wagner M, Khoury H, Rindress D, Gregoire JP, Deal C. Combining multicriteria decision analysis, ethics and health technology assessment: applying the EVIDEM decision-making framework to growth hormone for Turner syndrome patients. Cost Eff Resour Alloc 2010;8:4.

251. Briggs A, Sculpher M, Buxton M. Uncertainty in the economic evaluation of health care technologies: the role of sensitivity analysis. Health Econ 1994;3(2):95-104.

252. May C, Finch T. Implementation, embedding, and integration: an outline of Normalization Process Theory. Sociology 2009;43:535-54.

253. Chen CL, Tang FT, Chen HC, Chung CY, Wong MK. Brain lesion size and location: effects on motor recovery and functional outcome in stroke patients. Arch Phys Med Rehabil 2000;81(4):447-52.

254. Cummings T on behalf of the A Very Early Rehabilitation Trial Collaboration. Is early physical activity after stroke associated with cognitive function? A sub-study of AVERT. 2012. Available from: T. Cummings.

255. Harwood RH. Economic evaluations of complex services for older people. Age Ageing 2008;37(5):491-3.

256. Rowan KM, Kerr JH, Major E, McPherson K, Short A, Vessey MP. Intensive Care Society's APACHE II study in Britain and Ireland--II: Outcome comparisons of intensive care units after adjustment for case mix by the American APACHE II method. BMJ 1993;307(6910):977-81.

257. Hacke W, Kaste M, Skyhoj Olsen T, Orgogozo JM, Bogousslavsky J. European Stroke Initiative (EUSI) recommendations for stroke management. The European Stroke Initiative Writing Committee. Eur J Neurol 2000;7(6):607-23.

258. Van de Port IGL, Kwakkel G, Schepers VPM, Lindeman E. Predicting mobility outcome one year after stroke: a prospective cohort study. J Rehabil Med 2006;38(4):218-23.

259. Kaczmarczyk K, Wit A, Krawczyk M, Zaborski J. Gait classification in post-stroke patients using artificial neural networks. Gait Posture 2009;30(2):207-10.

260. Sundseth A, Thommessen B, Ronning OM. Outcome after mobilization within 24 hours of acute stroke: a randomized controlled trial. Stroke 2012;43(9):2389-94.

261. Canavero, Cavallini A, Bettoni M, Riva S, Quaglini S, Micieli G. The Effects and Risks of Early Mobilization After Stroke: data from the Lombardia Stroke Registry, 2012. Abstract presented at European Stroke Conference, Lisbon. Available from: http://www.esc-archive.eu.

262. Matsui H, Hashimoto H, Horiguchi H, Yasunaga H, Matsuda S. An exploration of the association between very early rehabilitation and outcome for the patients with acute ischaemic stroke in Japan: a nationwide retrospective cohort survey. BMC Health Services Research 2010;10(1):213.

263. Murray E, Treweek S, Pope C, MacFarlane A, Ballini L, Dowrick C, et al. Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. BMC Medicine 2010;8(1):63.

264. Riley T, Hawe P, Shiell A. Contested ground: how should qualitative

evidence inform the conduct of a community intervention trial? J Health Serv Res Policy 2005;10(2):103-10.

265. Ajzen I. The theory of planned behaviour: reactions and reflections. Psychol Health 2011;26(9):1113-27.

266. Rogers EM. The Diffusion of Innovations. 4th Edition. New York:Free Press;1995.

267. Green LW and Kreuter MW (1991). Health Promotion Planning: An Educational and Environmental Approach. Palo Alto: Mayfield Publishing.

268. Allaire AS, Labrecque M, Giguere A, Gagnon MP, Grimshaw J, Legare F. Barriers and facilitators to the dissemination of DECISION+, a continuing medical education program for optimizing decisions about antibiotics for acute respiratory infections in primary care: A study protocol. Implement Sci 2011;6:3. doi: 10.1186/1748-5908-6-3

269. De Vos ML, van der Veer SN, Graafmans WC, de Keizer NF, Jager KJ, Westert GP, et al. Implementing quality indicators in intensive care units: exploring barriers to and facilitators of behaviour change. Implement Sci 2010;5:52. doi:10.1186/1748-5908-5-52

270. Goderis G, Borgermans L, Mathieu C, Van Den Broeke C, Hannes K, Heyrman J, et al. Barriers and facilitators to evidence based care of type 2 diabetes patients: experiences of general practitioners participating to a quality improvement program. Implement Sci 2009;4:41.doi:10.1186/1748-5908-4-41

271. House of Commons Health Committee. Use of New Medical Technologies within the NHS. UK;2005. Available from: http://www.parliament.the-stationery-office.co.uk.